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Sheraton-Cleveland
Cleveland, Ohio
22, 23, 24, 25 October 1961

Course in Postgraduate Gastroenterology
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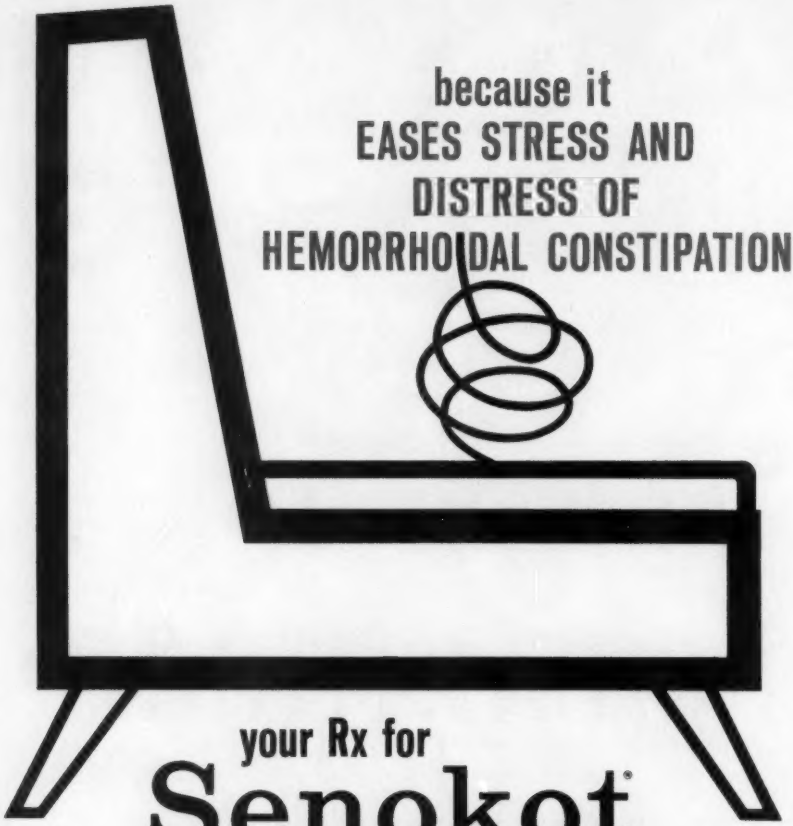

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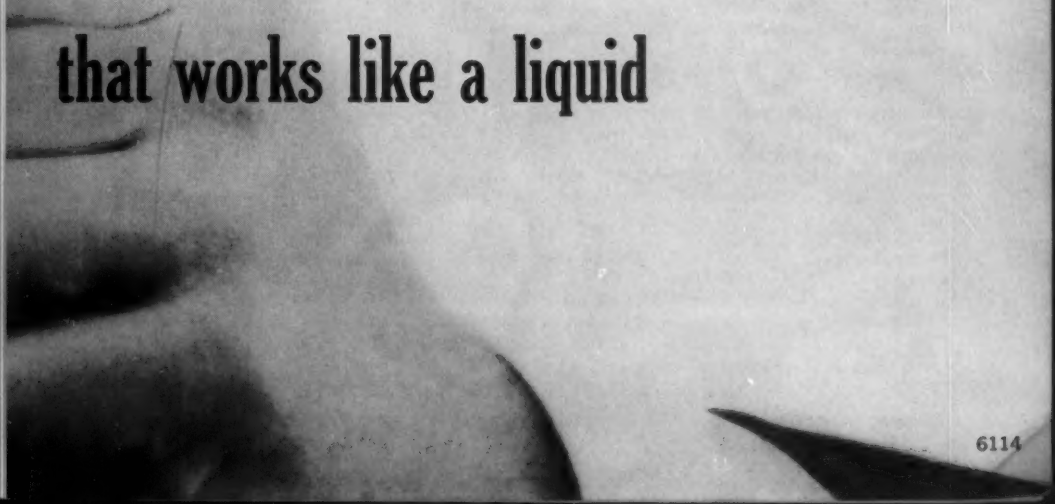

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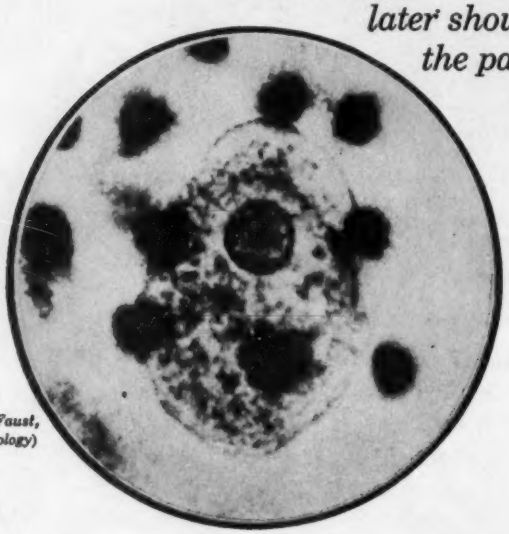

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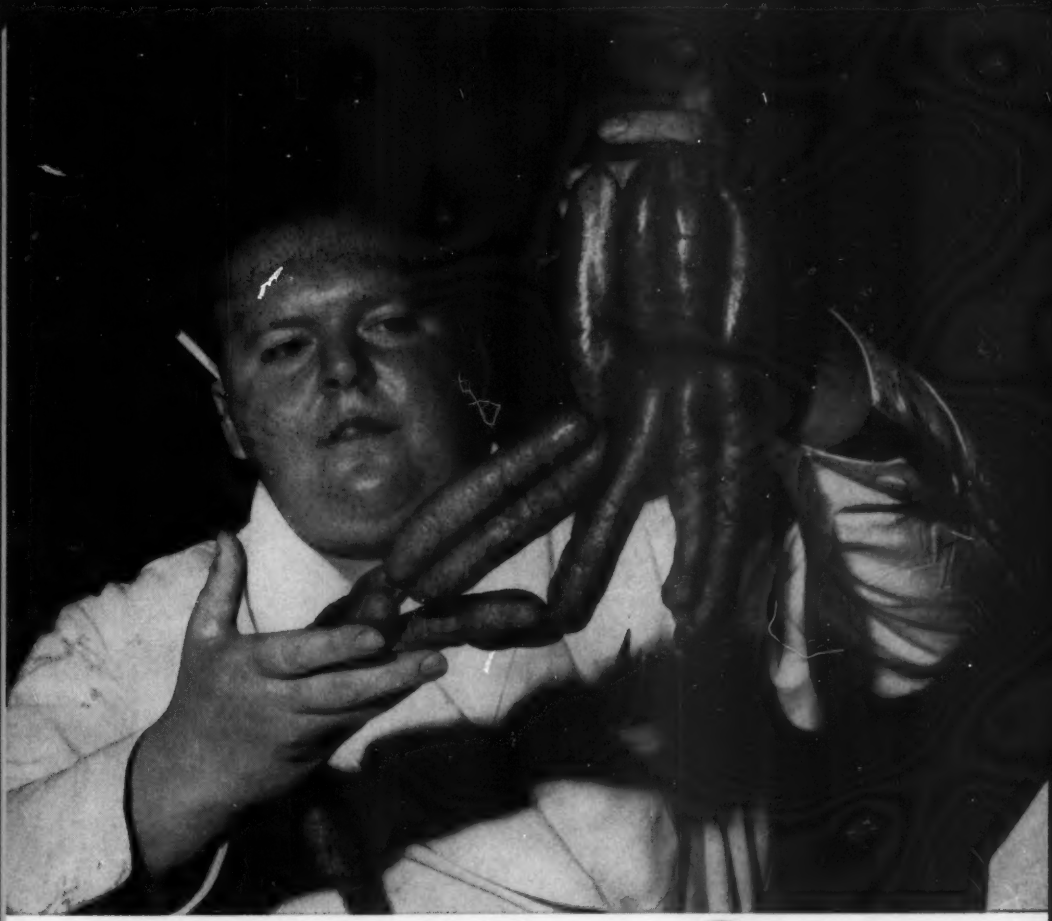

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VOLUME 36 SEPTEMBER, 1961 NUMBER 3

EXPERIENCE WITH THE LEUCINE AMINOPEPTIDASE ASSAY*

SEYMOUR WINSTEN, M.D.

Flourtown, Pa.

Clinical chemistry has made tremendous strides in recent years in the development of new diagnostic aids. Many chemical components of the blood and urine, that as little as ten years ago were looked upon as research curiosities, are now being routinely assayed in the chemistry laboratory. Perhaps the most startling developments have been in the field of enzymology. There is hardly a laboratory in the country, hospital or private, that at least once during the day does not do an assay for serum enzyme constituents. In almost every issue of every medical or surgical journal, we can read about a new enzyme procedure which appears to be a valuable diagnostic tool.

In March, 1958, a report of this nature appeared in *Cancer*. It described a colorimetric method for the determination of an enzyme that the authors, Goldbarg and Rutenberg, called leucine aminopeptidase[1]. Their method was a modification of a histochemical procedure which claimed a specific activity when the substrate was L-leucyl-beta-naphthylamide. This specificity has recently been challenged by Glenner, Burstone and Meyer[2]. Since the lack of specificity apparently does not affect the clinical evaluation of serum enzyme assay, we shall continue to call the serum enzyme, LAP. The initial report by Goldbarg and Rutenberg was soon followed by an interesting article summarizing their available data on patients with carcinoma of the pancreas[3]. It was the author's contention that if used in an intelligent manner, this determination, if performed serially would be a great aid in the diagnosis of carcinoma of the pancreas. At this point we became interested in this enzyme and began a series of studies with the view of determining whether we could corroborate their results and whether we should add this enzyme to our growing armamentarium of clinical chemistry assays.

The method we used was essentially the one described by Goldbarg and Rutenberg. It is based upon a hydrolytic activity of leucine aminopeptidase

*Presented before the Course in Postgraduate Gastroenterology of the American College of Gastroenterology, Philadelphia, Pa., 27, 28, 29 October 1960.

on the substrate L-leucyl-beta-naphthylamide. This results in the splitting of the molecule of the substrate and liberating the beta-naphthylamide, a compound which can be measured by a modification of the Bratton-Marshall reaction for sulfa compounds. We adapted a semimicro modification of the original methods. The normal range in our laboratory is between 50-200 units/ml. During our study we performed other serum enzyme determinations by conventional methods. The data chosen for this presentation was obtained from patients from which there were either surgical biopsies or autopsy specimens.

Our initial results indicated that extremely elevated levels of leucine aminopeptidase could be found in other conditions than carcinoma of the pancreas and we began to feel that the elevations were due primarily to some

TABLE I

CARCINOMA OF THE EXTRAHEPATIC BILIARY REGION

Patient	Primary	Bilirubin	Alk. PO_4	Highest Level			
				LAP	SGOT	SGPT	LDH
F.S. (A)	Pancreas	3.8- 5.9	31.2	900	66	48	250
A.D. (A)	Pancreas	10.5-18.2	42.2	530	194	71	1,000
H.B. (A)	Pancreas	11.3-18.0	20.4	600	65	85	500
I.M. (S)	Pancreas	2.0- 4.6	32.0	670	165	140	450
X.Y. (S)	Biliary tree	8.6-15.0	11.8	475	11	26	250
W.H. (S)	Pap. of Vater	4.6- 7.7	19.9	450	39	46	180
A.C. (S)	Pap. of Vater	9.6-18.8	30.6	700	700	630	920
C.C. (A)	Gallbladder	7.6-16.8	20.5	485	55	50	260
D.W. (A)	Lymphosarcoma (periportal)	10.5-18.2	42.2	530	8	4	100

(A) Autopsy (S) Surgical

liver involvement either from the presence of primary or secondary tumor masses in the liver or from partial or complete obstructions of the liver by an occluding primary tumor or calculi. Some typical results are shown in Table I. The cases chosen for presentation in this table all had levels greater than the critical level of 450 units/ml. Though we have had subsequent additional information, this table summarizes our findings with tumors of the extrahepatic biliary region. As you can see, there are four cases of carcinoma of the pancreas. In all four of these cases the elevations are above 450 units per ml. There are, however, five other cases with various types of malignancies and all have similar elevations. The alkaline phosphatase are also consistently elevated. There seems to be no relationship between elevation of SGOT, SGPT, and LDH and the clinical condition.

It was now evident to us that elevations above 450 units/ml. could be found in tumors of the extrahepatic biliary region without carcinoma of the pancreas. Since all these cases had pathologically demonstrable liver metastases, we began to review our data on patients without extrahepatic biliary tumors, but with autopsy or surgical evidence of liver metastases. Our next table (Table II) presents our results with ten patients of this type. In 9 of these cases there are elevated leucine aminopeptidase. One patient did not have an elevated leucine aminopeptidase, though an elevated alkaline phosphatase level was reported. The enzyme determination, however, was done six months before the autopsy evidence was obtained. At the time of the autopsy moderately diffuse nodular metastases were found in the liver. Though it is obvi-

TABLE II

ENZYME LEVELS IN LIVER METASTASES

Patient	Primary	LAP	Alk. PO_4	SGOT	SGPT	LDH
A.C. (A)	Prostate	137	9.3	—	—	—
W.C. (A)	Bronchogenic	248	9.8	8	26	550
V.B. (S)	Bronchogenic	475	13.0	120	22	2,000
W.T. (S)	Primary unknown	650	21.8	137	90	170
E.F. (S)	Breast	900	20.3	180	130	300
R.M. (S)	Breast	900	37.6	105	50	400
E.R. (S)	Melanoma	305	—	18	13	300
R.S. (A)	Melanoma	320	20.9	20	18	130
R.F. (S)	G.I. tract	1,430	32.6	20	57	180
A.W. (S)	G.I. tract	830	14.1	65	25	1,400

(A) Autopsy (S) Surgical

ous that the elevation of leucine aminopeptidase in three of the cases is not extensive, six patients with liver metastases from tumors from various sites have elevations of leucine aminopeptidase above 450 units/ml. At the present time, we have had ten additional cases with liver metastases from a primary source other than the pancreas, whose assay levels are greater than 450 units/ml. of leucine aminopeptidase. Subsequently, we will demonstrate the fact that the consistent serial elevations of leucine aminopeptidase can also be found in diseases other than carcinoma of the pancreas. Early in our study we observed a relationship between elevated leucine aminopeptidase levels and alkaline phosphatase and the pathological evidence of liver metastases. Table III summarizes the data on 30 cases of this type. In 12 cases with mildly elevated alkaline phosphatase, only five had elevations of leucine aminopeptidase above

450 units/ml. Eleven of these 12 patients had levels above 200 units/ml. In 18 other cases with alkaline phosphatase above 15 Bodansky units, 17 had extremely elevated leucine aminopeptidase levels. Though from this data it would appear that the degree of obstruction as reflected by the increased alkaline phosphatase activity is related to the elevation of leucine aminopeptidase, we

TABLE III

COMPARISON OF SERUM ALKALINE PHOSPHATASE AND LEUCINE AMINOPEPTIDASE LEVELS IN PATIENTS WITH LIVER METASTASES

Alk. PO_4 activity	LAP Level 50-200	LAP Level 200-400	LAP Level 400-500	Total Cases
5-15 BU	1	6	5	12
15-16 BU	0	1	17	18

have had several patients in which we did not see this relationship. These four cases are summarized in Table IV. In all of these patients there were initially anicteric sera but both the leucine aminopeptidase and alkaline phosphatase activities were above normal. In fact, extremely elevated levels of leucine aminopeptidase were found in all of these patients even though nonjaundiced serum specimens were obtained. Table V presents our data on patients with

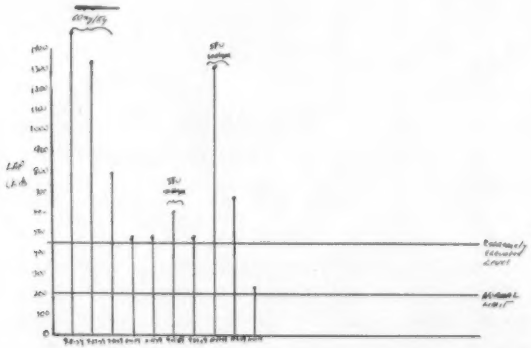

Fig. 1

elevated alkaline phosphatase and low or normal leucine aminopeptidase. In only one of these patients was there any evidence of liver involvement either clinically, surgically, or by laboratory data. This patient not only had Paget's disease but also cholelithiasis. This latter condition may have accounted for the slight elevation of leucine aminopeptidase. It may be possible to exclude the presence of liver metastases on the basis of a low leucine aminopeptidase

and an elevated alkaline phosphatase. Having observed the consistent relationship between the occurrence of liver metastases and the combined elevations of alkaline elevations of alkaline phosphatase and leucine aminopeptidase, and wishing to establish objective criteria for the evaluation of cancer chemotherapeutic agents, we began to assay these serum enzyme levels in patients under-

TABLE IV

LAP and Alk. PO_4 Activities in Relatively Anicteric Sera in Patients with Liver Involvement

Patient	Diagnosis	Bilirubin	LAP	Alk. PO_4
I.M.	Ca. of pancreas with liver metastases	0.5-0.8	510	18.0
R.F.	Ca. of G.I. tract with liver metastases	0.6-0.9	640	23.4
V.B.	Bronchogenic Ca. with liver metastases	0.2-0.8	475	13.0
F.C.	Hepatoma with bone metastases	0.5-0.9	730	14.7

going cancer chemotherapy. This study was done with the cooperation of the chemotherapy group at the Albert Einstein Medical Center under the direction of Dr. Irving Woldow with the close association of Dr. Stanley Levick and Dr. I. R. Schwartz. We have evaluated approximately 60 patients in this manner. During the course of our studies we were able to observe serial elevations in

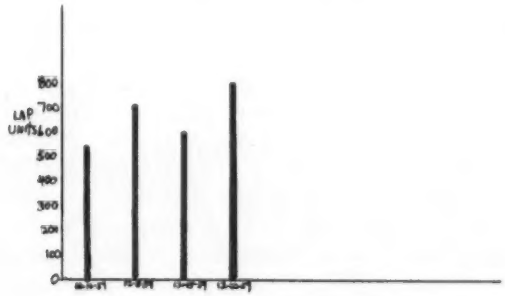

Fig. 2

patients whose diagnosis excluded carcinoma of the pancreas. In several of these patients with gastrointestinal malignancy, we obtained our highest levels of leucine aminopeptidase. A typical curve of a patient having a good response to chemotherapy is shown in Figure 1. As you can see there seems to be a definite drop in leucine aminopeptidase activity following therapy. This drop

was accompanied by an improvement in the clinical condition. As a need for a new regimen of therapy occurred, there was a rise of the leucine aminopeptidase level which invariably dropped after the therapy was given. The patient was still alive on 1 July 1960 and still fluctuating in his therapeutic course. Similar, though not as dramatic changes occurred when we followed the alkaline phosphatase levels.

Unfortunately, most of our cases did not give such a dramatic response and most of them fit the category demonstrated in data in Figure 2. There was little response to therapy and the patient eventually succumbed to his disease. We have also studied cases of patients having cholecystitis, choledocholithiasis, portal thrombophlebitis, cirrhosis, hepatitis, and children with biliary atresia. In almost all of these conditions we observed elevated levels of leucine aminopeptidase. There did not appear to be any constant significant trend by which this enzyme assay can be used to differentiate these various syndromes.

TABLE V

LAP AND ALK. PO_4 ACTIVITIES IN RELATIVELY ANICTERIC SERA IN PATIENTS WITHOUT LIVER INVOLVEMENT

Patient	Diagnosis	Bilirubin	LAP	Alk. PO_4
M.K.	Paget's disease and cholelithiasis	0.2 -1.2	240	49.7
A.H.	Carcinoma of prostate with bone metastases	0.4 -1.2	125	17.9
J.S.	Carcinoma of breast with bone metastases	0.07-0.3	143	30.7

In summary we would like to emphasize several points. It will appear that extreme serial elevations of leucine aminopeptidase activity is found in the sera of patients whose diagnosis excludes the possibility of a carcinoma of the pancreas. Recent reports, Arst and co-workers[4], Shay and his collaborators[5] seem to confirm this view. We feel further that the major value of this determination lies in the early detection of hepatobiliary disease, and the chemical corroboration of clinical evaluation of the presence of secondary liver metastases. Furthermore it would seem that serial study of serum leucine aminopeptidase levels could serve as an objective parameter for evaluation of the response to cancer chemotherapy.

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THE SURGICAL MANAGEMENT OF CHRONIC PANCREATITIS*

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In the early part of the present century, acute pancreatitis was treated surgically with a prohibtive mortality[11]. The concept of medical management of acute pancreatitis gained general acceptance in Europe and America by 1930 with a significant reduction in mortality. Acute pancreatitis can be managed successfully by nonoperative treatment, with few exceptions[5].

The management of patients with chronic recurrent pancreatitis has not shown the same success without operative intervention. Many of these patients continue to experience exacerbations of their disease despite medical therapy. Others are psychologically incapable of following any medical regime. Progressive diminution of pancreatic function occurs with increasing frequency and severity of attacks. Pain, the most important symptom of the disease, becomes relentlessly constant and frequently requires narcotics for control. This almost inevitably leads to addiction to narcotics or alcohol or both. Nutritional disturbances, diabetes, steatorrhea and other metabolic disorders lead to weight loss and extreme inanition. The chronic debilitating phase of recurrent pancreatitis, so aptly described by Longmire[26] becomes manifest. It is common for the clinical picture to resemble the cachexia associated with a malignant process.

The first recorded operation on the pancreas was performed in 1862, by LeDentu[25] who drained a pancreatic cyst. Unfortunately, the patient succumbed postoperatively from peritonitis. Twenty years later, Gussenbauer, a pupil of Billroth, successfully marsupialized a pancreatic cyst[19]. Since that time numerous operative procedures, based on sound physiologic principles, have been advocated for the treatment of chronic pancreatitis.

Opie[29] early associated biliary tract disease with recurrent pancreatitis. Archibald[3] and later Cameron and Noble[9] considered obstruction at the papilla of Vater with reflux of bile through a common channel into the pancreatic duct the most likely cause of acute recurrent pancreatitis. Reflux of bile into the pancreatic duct was thought to be caused most frequently by an impacted common duct stone or by spasm of the sphincter of Oddi. For this reason,

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cholecystectomy, common duct exploration and dilatation of the sphincter of Oddi seemed a reasonable procedure to insure adequate biliary drainage. Doubilet and Mulholland[14,15] advocated division of the sphincter of Oddi as a method of permanently preventing reflux of bile into the pancreatic ductal system. Bowers[7,8] and Allbritten[2] achieved complete diversion of bile by dividing the common bile duct proximal to its intrapancreatic portion and shunting the biliary drainage into the gastrointestinal tract by means of a Roux-en-Y choledochojejunostomy.

Fig. 1—Case 1, A.M., 29-year old colored woman. Postoperative T-tube cholangiogram showing free passage of dye into duodenum. Note pancreatic calcification.

In 1951, Longmire and Wallner[27] amputated the tail of the pancreas and anastomosed the proximal divided segment to the jejunum. This procedure was designed to provide retrograde drainage of a proximally obstructed dilated pancreatic ductal system. This did not result in relief of the patient's symptoms. Duval[16,17,18] however, obtained good results with caudal pancreaticojejunostomy with a Roux-en-Y anastomosis in an imposing series of cases.

Reinhoff and Baker, Smithwick, Pfeiffer and Hinton, Ray and Console and Coffey[12,30,35,37,39] advocated procedures other than drainage of the biliary and pancreatic systems for the control of the intractable pain of chronic pancreatitis.

These procedures included vagotomy, sympathectomy and excision of the splanchnic nerves. Though some of these operations resulted in relief of pain, they had no direct effect upon the restitution of pancreatic functions and pain frequently recurred. Longmire, Cattell, Whipple, Rhoads[11,26,36,44] and others have advocated pancreatic resection as a method of controlling the advanced or "burned-out" phase of chronic pancreatitis with extensive fibrosis and/or calcification. As experience with the disease has increased, many of the procedures have not proved suitable for all phases of chronic pancreatitis, and the variety of such operations attest to the inadequacy of rigid adherence to one particular operative procedure. The purpose of this paper is to stress the importance of individualization of the surgical approach to the pathologic process encountered in each case. Six cases of chronic recurrent pancreatitis are described and the surgical approach to each case is outlined.

Case 1:—A. M., a 29-year old colored woman was admitted to the Jefferson Medical College Hospital on 8 September 1953 complaining of severe epigastric pain, nausea and vomiting. She had experienced similar episodes of pain, anorexia, weight loss and fatigue for periods of two months prior to admission. She also complained of intermittent attacks of similar but milder pain for the previous ten years. She had been an alcoholic since the age of 16. Physical examination revealed an acutely ill woman with abdominal distention and epigastric tenderness. Her serum amalyase on admission was 400 units rising to 1,016 units on her third hospital day. The billirubin was 1.8 mg. per cent with a positive direct serum van den Bergh test. When the acute process had subsided, x-ray studies were performed. A deformity of the duodenum was demonstrated and a cholecystogram was normal. On 19 October 1953, laparotomy revealed a massive inflammatory reaction involving the liver, pancreas, gallbladder, stomach and duodenum. There were no biliary calculi in the gallbladder or common duct. The pancreas was firm and grossly nodular. Cholecystectomy, exploration of the common bile duct, transduodenal sphincterotomy with biopsy of the sphincter of Oddi and ampulla, and T-tube drainage of the common bile duct was performed. Histologic studies showed chronic cholecystitis and chronic inflammation of the ampullary mucosa. The patient had an uneventful postoperative course and was discharged on the 15th postoperatvie day, after a normal postoperative cholangiogram and removal of her T-tube (Fig. 1). The patient remained free of symptoms when last seen four years following operation.

Comment:—This is a case of chronic pancreatitis in an alcoholic patient with biliary tract disease and inflammation and spasm of the sphincter of Oddi. Relief of symptoms was obtained by cholecystectomy, drainage of the common bile duct and transduodenal sphincterotomy.

Case 2:—V. B., a 22-year old white man was admitted to the Jefferson Medical College Hospital on 30 July 1957. He complained of severe epigastric pain radiating to the back. The pain began approximately four or five days prior to admission.

One year prior to this admission, he was hospitalized following an automobile accident, during which the steering wheel of the automobile forcibly struck him in the epigastrium. At that time, he noted the onset of severe abdominal pain and a diagnosis of acute pancreatitis was made. His symptoms subsided in ten days. Recurrent attacks of pancreatitis, however, required six subsequent hospital admissions for treatment. During four of the hospital admissions x-ray studies, including an upper gastrointestinal series, barium enema and cholecystogram were negative. Persistent epigastric pain was present between

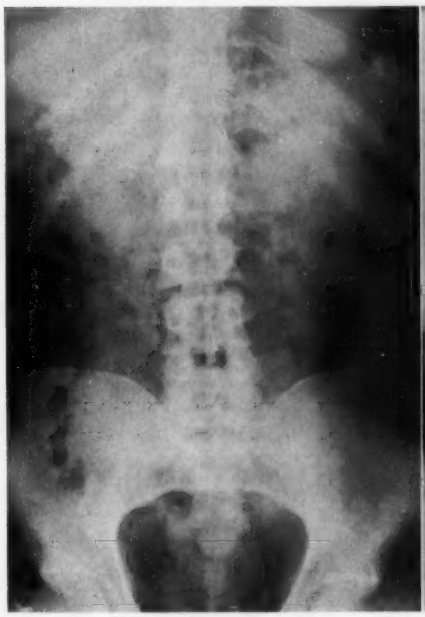

Fig. 2

Fig.3

Fig. 2—Case 3, C.W., 41-year old colored man. Plain film of the abdomen showing extensive calcification of the pancreas.

Fig. 3—Case 3, C.W., 41-year old colored man. Upper gastrointestinal series showing large filling defect in the gastric fundus. This was thought to be a carcinoma but proved to be a large pancreatic cyst.

each attack. Physical examination demonstrated marked abdominal tenderness and a large pulsitile mass in the mid-epigastrium. The serum amylase was 530 units. The patient's symptoms subsided following conservative therapy.

On 13 August, 1957, an exploratory laporotomy was performed and a large cyst of the pancreas was found overlying the vertebral body. Operative findings

suggested traumatic hemisection of the pancreas with diffuse chronic pancreatitis and cyst formation. A Roux-en-Y pancreaticocystjejunostomy was performed. The patient made an uneventful recovery and was discharged on the 11th hospital day. Since that time, he has gained 20 pounds in weight and was completely free of symptoms when examined in September, 1960.

Comment:—This represents a case of traumatic hemisection of pancreas with cyst formation, characterized by continuous epigastric and back pain with numerous attacks of recurrent pancreatitis. An excellent result was obtained by pancreaticocystjejunostomy.

Case 3:—C. W., a 41-year old colored man was admitted to the Veterans Administration Hospital on 5 June 1958, complaining of severe epigastric pain radiating through to the back. The patient had been a known alcoholic during the nine years prior to admission. He had suffered from recurrent attacks of a similar nature for ten years. The patient had numerous previous hospital admissions for recurrent attacks of pancreatitis.

The serum amylase was elevated to 900 units and a plain film of the abdomen revealed extensive calcification of the pancreas (Fig. 2).

On 28 May 1958, a cholecystectomy, common duct exploration and transduodenal sphincterotomy were performed and he made a satisfactory recovery. The postoperative cholangiogram was normal and the patient was discharged on 20 June 1958. He was readmitted on 12 July 1958, with recurrent abdominal pain, similar to his previous episodes. An upper gastrointestinal series revealed a filling defect in the fundus of the stomach (Fig. 3). He was thought to have a neoplasm of the gastric fundus. A left thoracotomy was performed on 13 August 1958. The defect in the fundus of the stomach proved to be a large cyst in the tail of the pancreas. A pancreaticocyst-gastrostomy was performed. The patient had an uneventful convalescence until 26 August 1958, when severe gastrointestinal hemorrhage occurred. The patient was re-explored and the bleeding site was found to be in the anastomosis. The shrunken pancreatic cyst was detached from the stomach and the gastric wall closed. The remaining portion of the cyst and the tail of the pancreas was amputated and the proximal end of the pancreas closed. He responded satisfactorily and was discharged on 21 September 1958. A gastrointestinal series was negative 3 months postoperatively. He has remained well and is gainfully employed. He was asymptomatic when seen in follow-up examination in March, 1960.

Comment:—This patient represents a case of chronic recurrent pancreatitis, which was not relieved by cholecystectomy and sphincterotomy. His symptoms persisted because of the pancreatic cyst. Decompression of the cyst into the stomach resulted in relief of his symptoms. Amputation of the decompressed cyst, together with the tail of the pancreas resulted in complete relief of his symptoms.

Case 4:—C. E., a 30-year old colored man was admitted to the Veterans Administration Hospital on 22 March 1959, complaining of severe recurrent epigastric pain, radiating through to the back. The patient had known chronic recurrent pancreatitis with extensive calcification of the pancreas. The patient first became ill with a right pleural effusion in February, 1957, for which he was later treated for tuberculosis. In January, 1958, he was operated upon for acute appendicitis and made an uneventful recovery. In the interval between January, 1958 and March, 1959, he was readmitted to the hospital four times with

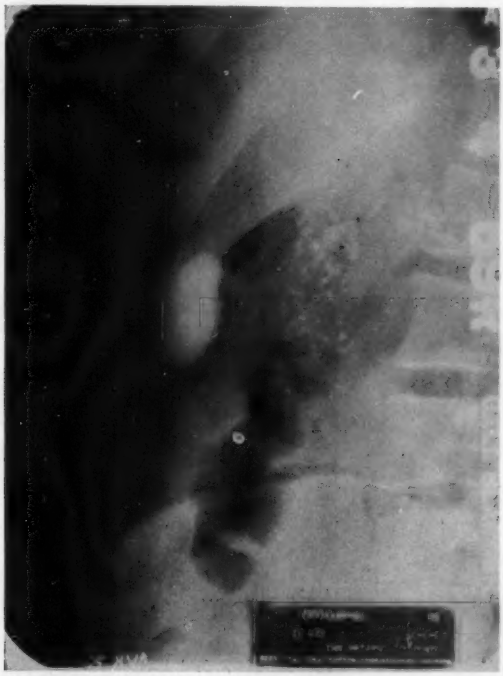

Fig. 4—Case 4, C.E., 30-year old colored man. X-ray shows good concentration of dye in the gallbladder. No stones are visible. Note extensive calcification of the pancreas.

recurrent attacks of pancreatitis. X-ray studies on each admission to the hospital, including cholecystogram, were normal except for extensive calcification of the pancreas and enlargement of the pancreatic head (Fig 4). Laporotomy was performed on 2 April 1959. The operative findings disclosed a cyst, 8 cm. in diameter, in the tail of the pancreas in addition to the extensive pancreatic calcification (Fig. 5). The biliary tract was free of disease.

The following procedures were carried out: Cholecystectomy, common duct exploration, sphincterotomy, caudal pancreatectomy, including the cyst, with

Roux-en-Y pancreaticojejunostomy. The patient made an uneventful recovery and was discharged on 10 April 1959. On 2 May 1960, he again suffered from abdominal pain and jaundice. He was readmitted to the hospital and intravenous cholangiography demonstrated narrowing of the intrapancreatic portion of the common bile duct (Fig. 6). His jaundice and symptoms subsided spontaneously and have not recurred subsequently. He has remained free of pain, has a good appetite and was gainfully employed when last examined in July, 1960.

Comment:—This patient represents a case of chronic recurrent pancreatitis with extensive calcification of the entire pancreas and a caudal pancreatic cyst. In addition to the cholecystectomy and common duct exploration with sphincterotomy, it was necessary to excise a cyst in the tail of the pancreas to provide adequate retrograde pancreatic drainage. The patient remained asymptomatic for 13 months following operation. He then experienced an attack of abdominal

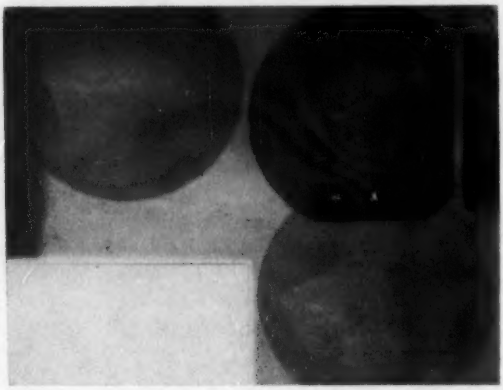

Fig. 5—Case 4, C.E., 30-year old colored man. X-ray of resected pancreatic tail injected with radiopaque dye. Note dilatation and ectasia of the pancreatic ducts.

pain and jaundice, which subsided in 2 days. An intravenous cholangiogram demonstrated narrowing of the intrapancreatic portion of the common duct. Combined sphincterotomy and caudal decompression of the pancreatic ductal system has thus far prevented further progression of his disease. Choledochojejunostomy may be necessary if further narrowing of the common bile duct occurs.

Case 5:—C. W., a 56-year old white man, was admitted to the Jefferson Medical College Hospital on 7 October 1959 because of severe abdominal pain radiating to the back. The patient was a known alcoholic for the previous 7 years and had innumerable attacks of abdominal pain, diagnosed, on several admissions as recurrent pancreatitis. The patient was known to have cirrhosis

of the liver. He required continuous administration of narcotics for control of his pain and had been unable to work for the preceding five years. Nine months prior to admission, he noted the onset of weight loss, polydypsia and polyuria. Examination by his physician disclosed diabetes mellitus. This became progressively severe and at the time of admission required 65 units of insulin daily for control. Physical examination revealed inanition, cachexia and abdominal tenderness. A plain film of the abdomen demonstrated extensive calcification of the pancreas (Fig. 7). Liver function studies showed marked impairment of hepatic function with 60 per cent BSP retention and a serum bilirubin of 2.5

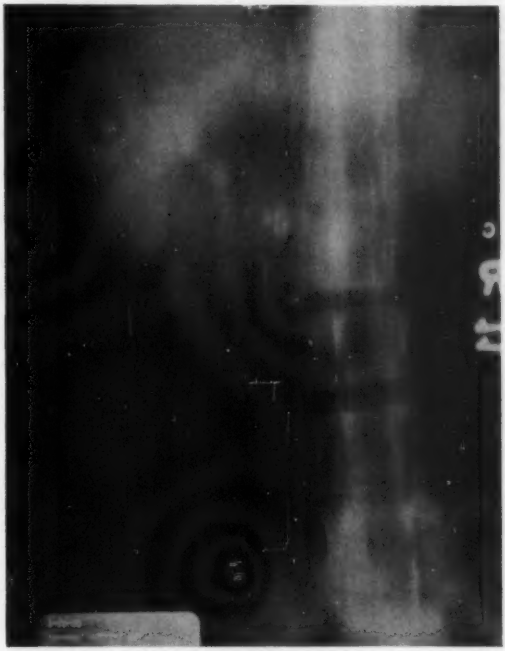

Fig. 6—Case 4, C.E., 30-year old colored man. Intravenous cholangiogram showing narrowing of the pancreatic portion of the comon bile duct.

mg. per cent. Laparotomy was performed on 26 October 1959. The pancreas was stony hard, the liver was nodular and the gallbladder was normal. Cholecystectomy, common bile duct exploration and transduodenal sphincterotomy were performed. Attempts to obtain an operative pancreatogram through the ampulla were unsuccessful because of obstruction of the duct of Wirsung. Amputation of the tail of the pancreas was done and an operative pancreatogram was performed through the dilated distal duct (Fig. 8). This showed a marked ectasia of the entire pancreatic ductal system and obstruction of the

pancreatic duct at the papilla of Vater. A Roux-en-Y caudal pancreaticojejunostomy was performed. Biopsy of the liver revealed chronic biliary cirrhosis.

The patient made a rapid recovery and was discharged from the hospital on the 13th postoperative day, free of pain and requiring no narcotics. He continued to improve and gain weight at the same time. His insulin requirements diminished progressively. Despite weight gain his diabetes was easily controlled on two tablets of Orinase daily. On follow-up examination in Sep-

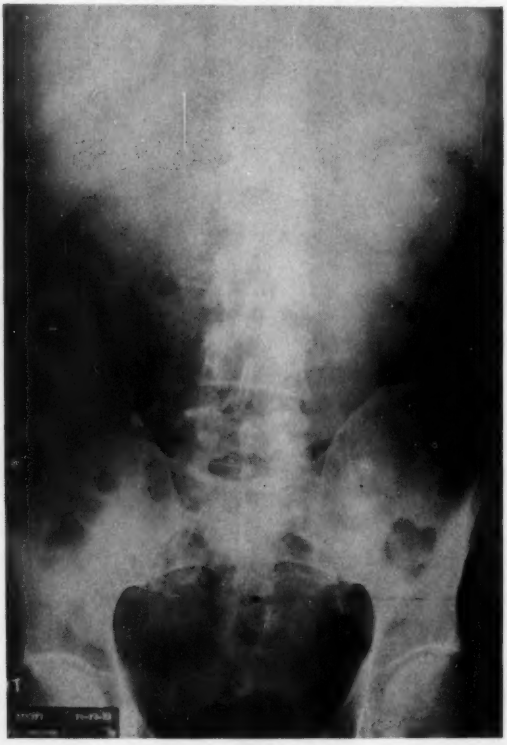

Fig. 7—Case 5, C.W., 56-year old white man. Calcification is noted throughout the entire pancreas.

tember, 1960, the patient had gained 25 pounds in weight, was completely free of symptoms and has been working steadily.

Comment:—This patient represents a case of chronic pancreatitis with diffuse calcification and complete obstruction of the proximal portion of the pancreatic ductal system. Cholecystectomy, common duct exploration and sphincterotomy would not have helped this patient, as determined by operative caudal

pancreatogram. Amputation of the tail of the pancreas with retrograde decompression into the gastrointestinal tract, provided adequate drainage and resulted in complete relief of the patient's symptoms.

Case 6:—J. B., a 56-year old white woman was admitted to the Jefferson Medical College Hospital on 24 October 1959, complaining of recurrent abdominal pain, localized in the left upper quadrant and radiating through to the back. Repeated x-ray and laboratory studies were negative. It was thought that the patient might be suffering from a tumor of the pancreas, because of the localization of her pain, its persistence and its radiation to the back. On 23 November 1959, the patient was operated upon. At the time of the operation the tail of the pancreas was enlarged, firm and nodular but did not contain cysts and was not adherent to surrounding structures. The head, neck and body of the pancreas felt soft and normal. The mass in the tail of the pancreas

Fig. 8—Case 5, C.W., 56-year old white man. Operative pancreatogram showing extreme dilatation and ectasia of the pancreatic duct system with cyst formation. There is complete obstruction of the ampulla of Vater.

was excised. An operative pancreatogram demonstrated complete patency of the pancreatic ductal system without obstruction or ectasia of the proximal pancreatic ducts (Fig. 9). Because this patient had developed chronic pancreatitis in the absence of biliary tract disease, the proximal end of the pancreas was anastomized to the jejunum by the Roux-en-Y technic. On the second postoperative day the patient developed abdominal pain and rigidity. The patient was re-explored and a perforated gastric ulcer was found and closed. Copious drainage was noted from the abdominal wound following the second operation. Ten days after the second operation, re-exploration was carried out. The pancreaticojejunostomy had failed to heal. The distal segment of the pancreas was reamputated and the pancreas closed. The defunctionalized jejunal limb was excised. Following this the patient made an uneventful recovery and has been completely free of abdominal pain or recurrent attacks. She was last seen in

follow-up examination in September, 1960. She has remained free of symptoms and has gained weight.

Comment:—The patient had chronic pancreatitis localized to the tail of the pancreas without biliary tract disease. Operative pancreatogram showed a normal remaining pancreatic ductal system. A sphincterotomy would not have been beneficial to the patient. In retrospect, excision of the diseased process in the tail of the pancreas would have sufficed.

Comment

There is persistent controversy concerning the etiology of chronic pancreatitis[3,9,22,29]. Most surgeons are in agreement that chronic pancreatitis associated with biliary tract disease responds quite well to correction of the biliary tract disease and the promotion of adequate biliary and pancreatic drainage. There

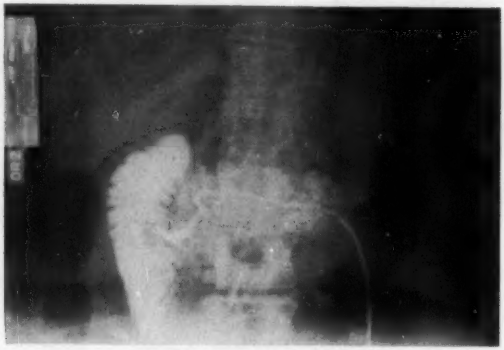

Fig. 9—Case 6, J.B., 56-year old white woman. Operative pancreatogram following resection of localized disease in the tail of the pancreas. The pancreatic duct system is normal and there is free passage of dye into the duodenum.

are major differences of opinion as to how best to provide adequate biliary and pancreatic drainage and prevent reflux of bile[24,31-34,40,41,43].

Considerable clinical and experimental evidence exists which supports the most commonly accepted theory that chronic pancreatitis is most frequently caused by obstruction at the sphincter of Oddi or the papilla of Vater or both. The procedure of sphincterotomy, first advocated by Archibald and Mullally[4] and Colp[13] and popularized by Doubilet and Mulholland[15] has been utilized frequently to correct the obstruction and reflux of bile and activated pancreatic juice. Refinements of this procedure in the form of sphincteroplasty and plastic procedures on the opening of the pancreatic duct by Jones and Smith[23], Nardi[28] and Bartlett[6], have resulted in wider application of this procedure.

Hill[20,21], however, has emphasized that such procedures are not likely to be successful in those cases where obstruction to the pancreatic duct occurs

distal to the ampulla and has utilized an operative pancreatogram to determine the status of the pancreatic ductal system and as a guide in the selection of a surgical procedure.

There is general agreement that patients with a history of alcoholism who develop chronic pancreatitis, do not respond as well to surgical treatment as those patients without this addiction[22], and that patients with chronic pancreatitis without associated biliary tract disease do not fare as well as a group, as those patients with chronic pancreatitis and associated biliary tract disease. There is considerable disagreement as to the best surgical procedure to be used in cases of chronic pancreatitis with pancreatic duct obstruction distal to the ampulla, with extensive calcification of the pancreas, with pancreatic duct calculi, or with the advanced stages of pancreatic fibrosis[1,10,11,26,38,42].

It is obvious that no one procedure provides the answer to the many complex pathologic states that may be encountered in patients with chronic pancreatitis. While caudal pancreaticojejunostomy may not be the procedure of choice in a patient with chronic pancreatitis and stenosis of the intrapancreatic portion of the common duct, choledochojejunostomy, a procedure which diverts the alkaline biliary drainage away from the duodenum, may be unsuitable in a similar patient with a history of duodenal ulcer, or as the first definitive procedure in a patient with chronic pancreatitis associated with correctable biliary tract disease.

Certain patients are best benefited by a combination of operative procedures either in stages or at one time. Caudal pancreaticojejunostomy has provided satisfactory decompression and retrograde drainage of an obstructed dilated pancreatic duct with the site of obstruction at the papilla. In certain instances it may be advantageously combined with correction of biliary tract disease and sphincterotomy or sphincteroplasty. Partial resection of the pancreas may be combined with one of the various drainage procedures, depending on the presence of absence of cysts, extensive fibrosis or calcification and the demonstration of obstruction of the pancreatic duct by operative pancreatogram. More radical resection, including pancreaticoduodenectomy or total pancreatectomy may be resorted to as procedures of last recourse in isolated instances.

Summary

1. Patients with chronic pancreatitis rarely respond to medical treatment alone and require surgical intervention to interrupt the progress of the disease and relieve their symptoms.

2. Numerous operative procedures have been advocated for the treatment of chronic pancreatitis.

3. Six cases of chronic recurrent pancreatitis are described and the surgical procedure used in each case is outlined.

4. The importance of individualization of the surgical approach to the pathologic process encountered is discussed.

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Discussion

Dr. C. Wilmer Wirts (Philadelphia, Pa.):—I think all physicians are extremely conscious of the difficulty encountered in diagnosing and treating pancreatic disease, thinking in terms of the exocrine portion of the gland. We have had two presentations this morning, one dealing with diagnosis and the other dealing with therapy. There is a great deal more to be said from the standpoint of diagnosis than Dr. Winsten was able to encompass and his remarks were confined to one of the most recent enzyme tests, leucine aminopeptidase. I believe, as he pointed out, this is now generally looked upon as being insufficiently specific to be employed with any great feeling of security that an abnormality represents specifically pancreatic disease. It may, unfortunately, represent biliary tract disease, hepatic disease, duodenal disease, or a combination of pancreatic or duodenal or biliary disease. Probably it has some merit in the diagnosis of

chronic pancreatitis, if other causes of the patient's symptoms can be excluded. It still, however, represents what we might call a guess rather than a specific diagnostic test.

I do not believe the evaluation of a patient with acute pancreatitis should give the physician much difficulty, if he bears the possibility in mind and has available the serum amylase test. Fortunately this test is simple, and available in most every institution, but I would warn you that it must be utilized on an emergency basis and therefore be available 24 hours a day. If it shows distinct elevation it is seldom that the pancreas is not involved in a disease process. It is true that individuals who have impaired renal function or certain viral infections, particularly mumps, may have an elevation of the serum amylase without it indicating primary pancreatitis, but I believe the clinical condition should be sufficiently suggestive that one need not be confused.

Conditions requiring consideration for differential diagnosis include many abdominal catastrophies such as a perforated peptic ulcer, intestinal obstruction, mesenteric thrombosis and, in the female—I am very sensitized to this diagnosis having encountered the problem of diagnosing it this past week—a ruptured ectopic pregnancy can all readily simulate acute pancreatitis.

The most frequent condition that one encounters today in the way of catastrophic illness that might offer confusion would be a coronary occlusion, or acute myocardial infarction. Here I believe the serum amylase test can be of the utmost help in making an early differential diagnosis. Other tests that one would employ, of course, would be the routine blood count, urinanalysis, a plain film of the abdomen and chest and an electrocardiogram. These studies are obtainable on an emergency basis and not too complex to request in any hospital. Is correct diagnosis important? It can be life-saving. I think we are all agreed that acute pancreatitis should be treated without operative intervention unless there is a complication such as abscess or cyst formation which is perpetuating the symptomats.

When we turn to the problem of chronic pancreatitis, we are confronted with a more difficult problem because there is no single test that has specificity and simplicity.

Again, the physician must remain constantly aware that if a patient has persistent upper abdominal pain particularly with reference around or through to the back for which one cannot find another ready explanation it would be wise to consider pancreatic disease as the cause of the patient's symptoms.

Again, just this past week I had the opportunity of seeing a patient who, for the past six months, has been treated as having symptoms from hiatal hernia in spite of the fact that she required narcotics for the relief of her pain and was losing weight so rapidly that in this six months period she had lost 38 pounds. Instead of considering cancer of the pancreas, which it was ultimately shown to

be, as a possible diagnosis, she was treated by having a phrenic crush performed. This, to my mind, is pursuing a possible diagnosis which after six months was no longer tenable. In fact it should not have been tenable after a much shorter period.

The diagnosis of chronic pancreatitis and neoplasm of the pancreas need not be made within 24 hours as it is desirable to do in acute pancreatitis, but, on the other hand, it is not normal, it seems to me, to expect a patient to have such persistent severe symptoms for weeks to months without the physician considering the possibility of disease of the pancreas.

What should one do then to get objective data? Of course, if the disease is in the head of the pancreas and jaundice develops, one's attention is more readily drawn to this possibility.

In the case of chronic relapsing pancreatitis, if one bears the possibility in mind and draws a sample of blood for the determination for serum amylase, serum bilirubin and glucose and finds a transient elevation of these values, it may be of help in diagnosis. Unfortunately, in the majority of instances, the physician may not have the fortuitous opportunity of seeing the patient just at the right time.

The x-ray examination of the abdomen showing calcification in the region of the pancreas is of great significance and the examination of the stool showing increased fat and meat fibers is important. A diabetic-type glucose tolerance test associated with pain should suggest more than simple diabetes mellitus.

Other tests are available and have been commented upon in the past, such as the Vitamin A tolerance test, the starch tolerance test and even the leucine aminopeptidase test. Unfortunately these are a bit complicated for routine use in view of the nonspecificity of the results. On the other hand, I would call your attention to the usefulness of the secretin test. The test has been available for many years, but has received varying degrees of enthusiastic use in the past largely because it is relatively complicated to perform and because of the lack of a consistent supply of the hormone. As you know, this test requires the passage of a double-lumen gastroduodenal tube under fluoroscopic control and the intravenous administration of the hormone secretin; collection of the duodenal secretions and measuring of the volume, bicarbonate value and enzyme content. Not the least important part of the secretin test is the availability today of cytologic examination for the diagnosis of cancer. This is time-consuming, expensive and, if one does not have a background of experience, there may be some limitations in one's ability to interpret it. There are, however, certain centers, and there should be more, where this test is made available. If doubt remains after the practicing physician has exhausted his diagnosis armamentarium I think it would be to his advantage to keep the secretin test in mind.

I will now ask Dr. Sterling if he would be willing to make some comments in this regard. Thank you very much.

Dr. Julian A. Sterling (Philadelphia, Pa.):—Fifteen years ago we could discuss the problem of pancreatitis and end in a United Nations frenzy of arguments. Today the question of pancreatitis has resolved itself fairly well because the medical man has admitted that pancreatitis is like your wedding anniversary: it is always with you but you frequently forget it. In any case, today we recognize a lot about the pancreas which we did not recognize before. For example, the term "ampulla" is returning to its proper place, to be forgotten. There is no ampulla at the end of the bile duct; it is a mass of tissue. That is the reason why today the sphincterotomy recommended by Doubilet, and that recommended by Archibald many years ago as a common duct sphincterotomy, has been replaced by either a combined pancreatic duct and common duct sphincterotomy or pancreatic duct sphincterotomy in those cases where there is occlusion to the pancreatic duct.

I would like to emphasize several facts: First, that Dr. Haupt pointed out to you how the clinical course of pancreatitis is variable; second, that it can be due to from 65 to 75 different causes; third, although Dr. Haupt indicated to you a half a dozen surgical procedures, I can tell you that there are at least 25 surgical procedures, and probably another 50 medical phases in management. So, variability is part of pancreatitis.

Now we are gradually narrowing down the problem in treatment of pancreatitis because we are beginning to recognize its various phases and its differing manifestations. The problem of pancreatitis, when it is uncomplicated, is to be thought of—in rule of thumb—as being "medical". When pancreatitis becomes complicated, then you begin to think of surgical help, just as, for example, you think of surgical help in cases of complicated peptic ulcers and diverticulitis. The uncomplicated peptic ulcer, the uncomplicated diverticulitis, the uncomplicated pancreatitis, these diseases are medical diseases. When they become complicated by pain, obstruction, hemorrhage or intractability, then keep in mind that these then become surgical problems. That does not always hold. I am just giving you a general rule which is subject to individual variations.

The problem of diagnosis of pancreatitis is such that we cannot make a clinical differentiation amongst edema, hemorrhage, necrosis and tumor in many patients. The value of our laboratory data and of clinical signs is variable, just as the individual patient is a variable. Here is where your astute and careful clinical observation repeated over hours and over days and possibly over weeks will give you a specific answer as to the patient's disease.

Dr. Wirts indicated that it is a confusing picture, that pancreatitis can mimic almost everything including hiatal hernia. Let us not be confused, let us try to clarify the diagnosis in our own mind on the basis of individual observation using every possible means to establish not only the diagnosis but also the course of the disease. Keep in mind one other thing: the patient with pancreatitis is unfortunately subject to recurrence. Whether it be "recurrent

acute" or "chronic relapsing" depends on what part of the country you are from or what disease you are trying to identify. There are many ways of handling the problem, many of them successful, some of them not.

Certain tests, as indicated by the essayists, including the Papanicolaou stain of drainage from the duodenum are valuable. Frequently our pathologist will say there are abnormal cells and we go in and find nothing at operation. Frequently he will say it is normal and we find tumor in the papilla or of the pancreas.

In this area, the differential diagnosis may have to be made at operation. The management of the patient with pancreatitis has to be supervised carefully by a gastroenterologist who is also a very careful clinician.

I would like at this point to ask the speakers to answer some questions. Dr. Winsten, there are a couple here, would you come here for a moment.

The first question asked, for your discussion, is something that Dr. Wirts touched upon also. "Would you clarify the problem of leucine aminopeptidase with reference to its being a hospital procedure? Can this be done, how difficult is it and is it a really formidable procedure for the hospital laboratory?"

Dr. Seymour Winsten (Flourtown, Pa.):—Actually, it is not a formidable procedure; it is no more formidable, I think, than some of the routine enzyme determinations that are performed nowadays. You need two instruments to do the determination, a colorimeter or spectrophotometer to read your result and a water bath at a constant temperature to incubate your reaction. It is not a difficult procedure. The method for it has been published in the literature. (We have made some slight modifications.) I am sure that any capable chemist will be able to handle the determination.

Dr. Sterling:—Dr Winsten, there is one other point. You possibly did not have time to discuss this, but would you indicate the other diseases in which the leucine aminopeptidase may be elevated? In other words, with reference to differential diagnosis, when the LAP is, for example, over 250 or over 500, how often do you look for other disease and what other disease could there be?

Dr. Winsten:—We have found elevations of leucine aminopeptidase above the 250 or 200 range in almost every type of liver disease. The elevations do not appear to have any relationship to the severity of type of disease. We have observed elevations in hepatitis, cholelithiasis, and choledocholithiasis. We, in fact, have done some studies on Dr. Sterling's patients, children with biliary atresia and have found elevations of leucine aminopeptidase. In acute pancreatitis, we have seen elevations of leucine aminopeptidase of about 300 to 400. Some patients with cirrhosis also had increased leucine aminopeptidase levels. Invariably though, the highest elevations occurred when there was some malignant process and the subsequent appearance of liver metastases.

Incidentally, of course, elevated leucine aminopeptidase has been reported in women who are in their second and third trimester of pregnancy. This increase of leucine aminopeptidase appears to have no relation to the development of jaundice in these patients.

Dr. Wirts:—Thank you. I think we have now seen the development of a new test for pregnancy.

Dr. Winsten:—This is only in the third trimester.

Dr. Sterling:—In any case, I think it might be fair to say that with certain exceptions, possibly specifically that relating to metastatic disease in the bone, that elevations of the LAP probably go hand-in-hand with, or are equivalent to elevations in the alkaline phosphatase. That is not entirely true, but it is sufficiently true—am I right, Dr. Winsten?

Dr. Winsten:—Yes.

Dr. Sterling:—It is sufficiently true that the significance of the LAP is not quite as we thought it was some years ago as indicative of diagnosis of carcinoma of the pancreas. It, however, is a valuable test for enzyme function within the liver and does indicate aberrations as being present. It, however, is not diagnostic. Is that generally true?

Dr. Winsten:—Yes.

Dr. Sterling:—Dr. Haupt, there are a couple of questions for you. Would you mind coming up, please? One of the questions that the doctors are interested in is with reference to the technics of pancreatogram. Does this harm the patient or is it really as valuable as it appears?

Dr. George J. Haupt (Philadelphia, Pa.):—In my opinion, it is an extremely valuable test. We feel generally that chronic recurrent pancreatitis is basically two diseases: one primarily due to biliary tract disease, and the other due to primary pancreatic disease, pancreatic lithiasis, obstruction of the pancreatic duct, etc. The purpose of presenting these six cases was to show the variance in operative findings and a plea to individualize the operative procedure and to restore as much as possible the function of the pancreas on a physiological basis.

Pain can be controlled if the obstructed ducts are decompressed.

Operative pancreatogram is quite easy to perform. A small polythene catheter is placed through the ampulla of Vater into the pancreatic duct. If this shows obstruction at the ampulla as in one case with marked ectasia of the pancreatic ducts, then, a caudal pancreatectomy should be performed. A small segment of the tail of the pancreas is removed, and usually one finds a large dilated duct that is easy to cannulate and a retrograde operative pancreatogram can be performed. I have found no harm from this procedure and it will help determine what should be done next.

If there is demonstration of the whole pancreatic ductal system up to the ampulla, I think that one can be reasonably sure that the operation of caudal pancreatic jejunostomy will adequately decompress the entire pancreas. If, however, there is a stone lodged at the angle of the duct of Wirsung so that there is obstruction at this point, then I think a sphincterotomy and caudal pancreaticojejunostomy are both indicated.

An operative pancreatogram is the best method of determining where the obstructive site or sites are and one must be persistent to relieve all segments of the obstructed ductal system, even to the point, of longitudinally opening the pancreatic duct. No operation should be done routinely but should be tailored to fit the physiologic restitution of pancreatic function.

Dr. Sterling:—Thank you, Dr. Haupt. Just one more thing. You touched on a point that one of the individuals would like, I think, to have amplified.

I am not going to say anything about the fact that you are talking about an ampulla which I do not happen to think exists, but that makes for better breakfast, I think. In any case, the problem raised by one of the other questions was: "Are there any specific procedures that you can do for relief of pain?" Now, you did mention local procedures. I think the question may have reference to extrapancreatic methods for controlling pain. Would you like to comment upon that, please?

Dr. Haupt:—Reinhoff and others have advocated vagotomy, sympathectomy, etc., for the relief of pain. It has been found also that advocates of pancreatic resection, have effected a relief of pain. These patients are theoretically mild diabetics after total pancreatectomy, requiring perhaps 40 units of insulin, but they are extremely unstable. A recent report has shown that a high percentage of such patients are either in serious difficulty or have died because of complications following the very unstable diabetes associated with total pancreatectomy.

BILIARY DYSKINESIA—REPORT OF TWO CASES WITH PHYSIOLOGIC STUDIES*

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Biliary dyskinesia is a term apparently first used by Westphal[1] to denote a widespread disruption of autonomic nervous activity leading to functional disturbances of gallbladder evacuation as well as of other gastrointestinal activities. His theories were based on a relatively small amount of clinical investigative work and the syndromes he described were not sharply defined. Biliary dyskinesia has come to mean different things to different physicians. Other terms have been used to describe disorders of gallbladder evacuation. Among them are biliary dyssynergia, the infundibulo-cystic syndrome and cystic dyskinesia. The differences in semantics are compounded by difficulties in diagnosis, specifically the inability by usual clinical means to establish an isolated defect in the emptying mechanism of the gallbladder. As the result of this confusion, many patients have undergone needless cholecystectomy for aerophagia which was mislabeled as biliary dyskinesia, while others have been denied treatment for bona-fide disease of the biliary tree and have been labeled psychoneurotics.

Normally, the gallbladder empties in response to the ingestion of food and the action of a hormone, cholecystokinin, released from the mucosa of the upper small intestine in response to food. The act of gallbladder evacuation, initiated by cholecystokinin, is effected by a complex neuromuscular mechanism in which there is simultaneous relaxation of the sphincter of Oddi and contraction of the gallbladder. Either organic obstruction of the biliary passages, from the infundibulum of the gallbladder down to the sphincter of Oddi, or disturbances in the neuromuscular mechanism may lead to impaired gallbladder evacuation. European and South American authors have customarily included both organic and functional causes of impaired gallbladder evacuation in the syndrome of biliary dyskinesia. In this country, the term has often been restricted to purely functional abnormalities.

The authors have recently studied two patients with impaired emptying of the gallbladder and wish to report their experience in the diagnosis and treatment of these patients.

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Case 1:—This 31-year old white, married, woman (A.H.) was admitted to the Jefferson Medical College Hospital on 1 September 1959 with severe abdominal pain. The patient gave a 10-year history of frequent nausea and right upper quadrant abdominal pains which occurred usually 1 to 2 hours after meals. The patient also complained of lower abdominal distress and diarrhea consisting of 3 daily stools which were soft and mixed with mucus. Complete diagnostic studies, including radiographic examinations of the gallbladder and gastrointes-

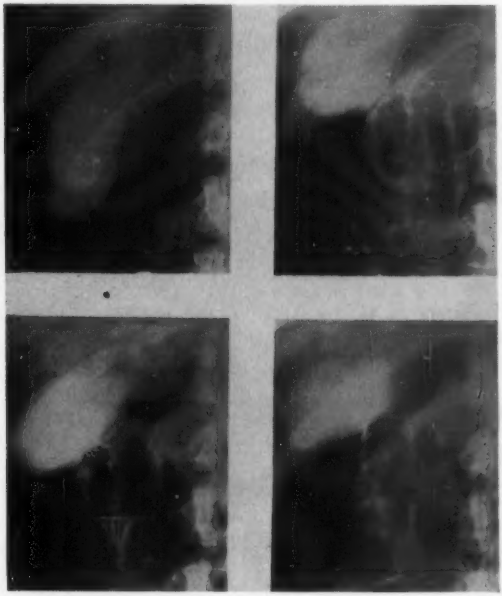

Fig. 1—Special cholecystographic study in patient A.H.
Upper left, control film showing large filled gallbladder.
Upper right, exposure taken 5 minutes after injection of cholecystokinin showing globular shape of gallbladder but no significant decrease in total volume.
Lower left, exposure taken 13 minutes after cholecystokinin injection and 3 minutes after sublingual nitroglycerine administration showing slight decrease in gallbladder size.
Lower right, exposure taken 20 minutes after injection of cholecystokinin showing no further significant decrease in gallbladder size.

tinal tract, had been performed 10, 6, and 3 years earlier. The tests were reportedly negative and the patient was advised to undergo psychiatric treatment. Antispasmodics and sedatives had provided transient and only partial relief of symptoms.

The past medical history included bilateral scalenectomies for cervical ribs in 1958 and June of 1959. The patient had successfully completed 3 pregnancies.

Physical examination revealed a well developed, somewhat hypersthenic, woman who was in moderate distress on admission. Temperature was 99 degrees, pulse was 80 per minute and blood pressure was 110/70. There were no abnormalities of the head, neck, chest, heart, or extremities. The abdomen was not distended and peristalsis was normal. There was tenderness over the right upper quadrant with moderate guarding but no rigidity. After the patient was able to relax, a distinct mass could be felt and was thought to represent a distended gallbladder. Rectal examination was normal.

Laboratory tests were as follows: Hemoglobin, 12.7 gm. per 100 ml.; leucocyte count was 6,500 with a normal differential count; urinalysis was normal; serum bilirubin was 1.9 mg. per 100 ml. total, 0.1 mg. direct reacting; serum amylase was less than 80 Somogyi units and serum lipase was 0.32 units per 100 ml. Radiologic examinations of the chest, upper gastrointestinal tract and gallbladder were reported as normal.

On 4 September 1959, a biliary drainage was performed with cholecystokinin as the stimulant of gallbladder evacuation. Shortly after the intravenous injection of 70 units of cholecystokinin, the patient developed a feeling of nausea, epigastric fullness and mild pain resembling her spontaneous postprandial pains. There was no bile flow for 10 minutes after the injection; thereafter about 100 ml. of very dark bile was collected. Concomitantly with the egress of bile, the right upper quadrant mass decreased in size but remained palpable and tender. Microscopic examination of bile disclosed no cholesterol or calcium bilirubinate crystals.

On 5 September, during a period of severe postprandial pain, the patient was given a sublingual tablet of nitroglycerine, grains 1/150. The pains ceased within 2 minutes; the gallbladder decreased in size but remained palpable. Pain recurred the following morning after breakfast and was again relieved by nitroglycerine.

The patient was next prepared for another radiologic examination of the gallbladder. Six tablets of Telepaque® were given on the evenings of 6 and 7 September. Fatty foods and nitroglycerine were withheld. On 8 September, a scout film of the right upper abdominal quadrant was taken, showing the size and shape of the filled gallbladder. Cholecystokinin (70 units) was injected intravenously between 11:52 and 11:55 A.M. Films were taken 2, 5, 10, 13, and 20 minutes after the completion of the injection. After the 10-minute film was taken, the patient was given a sublingual tablet of nitroglycerine for the relief of pain and nausea produced by the cholecystokinin injection. Inspection of the films (Fig. 1) disclosed a change in gallbladder shape from an elongated to a more globular configuration and a decrease in size of about 30 per cent, most of the decrease occurring after the administration of nitroglycerine.

On 10 September, the patient was operated on by one of us (R.G.J.). The gallbladder was found to be markedly enlarged but could be emptied by manual

compression. The cystic duct was folded on itself in an S-shaped curve, bound down firmly by scar tissue, (Fig. 2). The common duct was dilated to about twice the normal size. It was opened and through it the ampulla of Vater was explored. The sphincter permitted passage of no larger than a 2 mm. probe. A transduodenal sphincterotomy and a cholecystectomy were then carried out. Histologic examination of the gallbladder revealed findings of a mild chronic cholecystitis and pericholecystitis.

After an initial stormy postoperative course, the patient fully recovered and has remained free of her previous symptoms over a follow-up interval of one year.

Case 2:—This 40-year old married Negro woman (E.W.) was admitted to the Jefferson Medical College Hospital on 16 November 1959 with the complaints of right upper quadrant abdominal pain radiating around to the back and associated with nausea and vomiting. These symptoms occurred usually

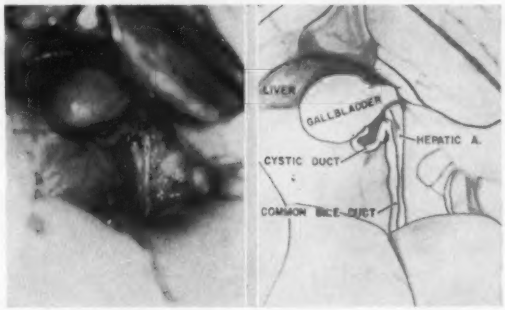

Fig. 2—Photograph and schematic drawing of operative findings in patient A.H., showing distended gallbladder and tortuous cystic duct. Picture taken after lysis of adhesions.

within 15 minutes to an hour after meals and lasted up to an hour. The patient first experienced the above symptoms about a year before admission. They initially tended to occur sporadically but during the month preceding admission followed practically every meal. The patient was afraid to eat, often skipped meals in order to avoid the pain, and had lost 15 pounds of weight.

The patient had previously been in good health. She had completed 5 pregnancies and had on miscarriage.

Physical examination revealed a well developed and well nourished woman in mild discomfort. Her temperature was 98 degrees, pulse was 80 per minute, and blood pressure was 120/70. No abnormalities were found on examination of the head, neck, chest, heart, or extremities. The abdomen was soft, not distended; peristalsis was normal; no masses or organs were palpable. There was tenderness in the right upper abdominal quadrant.

Laboratory tests were as follows: Urinalysis was normal; hemoglobin was 9.4 gm. per 100 ml.; leucocyte count was 4,500 per cu. mm. with a normal differential count; serum bilirubin was 0.4 mg. and 0.06 mg. per 100 ml. direct reacting; cholesterol was 223 mg. per 100 ml. The remaining liver function tests were normal, as were the serum amylase and lipase. Radiologic examinations of the chest, gastrointestinal tract and gallbladder were reported as normal.

On 23 November, a combined biliary drainage-secretin test was performed. Following the intravenous injection of 70 units of cholecystokinin, there was

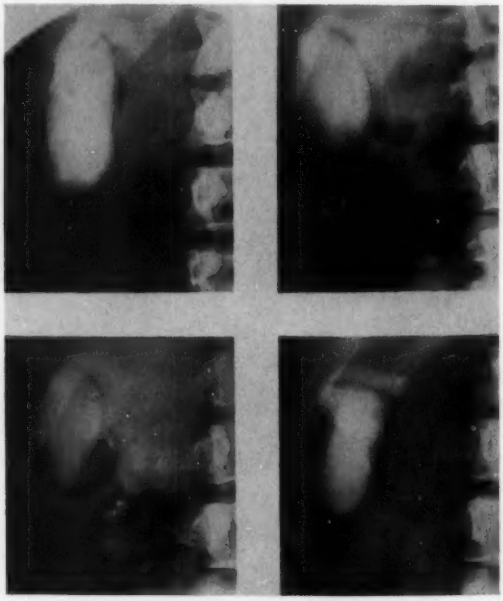

Fig. 3—Special cholecystographic study in patient E.W.
Upper left, control film showing large relaxed gallbladder.
Upper right, exposure taken 5 minutes after the injection of cholecystokinin showing change in shape of gallbladder and slight decrease in size.
Lower left, exposure taken 10 minutes after cholecystokinin injection showing further slight reduction in gallbladder size.
Lower right, exposure taken 45 minutes after cholecystokinin injection showing persistent large gallbladder shadow and sharp angulation between dilated neck of the gallbladder and narrow cystic duct.

marked delay in the appearance of bile. The patient's usual right upper quadrant pains were reproduced by the injection. During the 60-minute period of observation following the injection of secretin (given 10 minutes after the injection of cholecystokinin), there was continuous flow of bile indicative of impaired gallbladder function. Pancreatic function was normal as evidenced by

a normal volume and a normal bicarbonate concentration of 96 mEq./l. No cholesterol or calcium bilirubinate crystals were detected in the bile.

On 27 November, the radiologic examination of the gallbladder was repeated. The patient was given 6 tablets of Telepaque the preceding evening. A scout film of the right upper quadrant was taken in the supine position and the patient was then given 70 units of intravenous cholecystokinin. Supine films were taken at 2½, 5, 7½, 10, 15, and 45 minutes after the injection. There was gradual, limited decrease in the size of the gallbladder with an early change to a globular shape. The neck of the gallbladder and the proximal cystic duct were dilated; there was an abrupt change in the caliber of the distal cystic duct which was very narrow (Fig. 3). The patient experienced her usual discomfort during the test.

Laparotomy was performed on 3 December (by Dr. Nicholas J. Pozza). The gallbladder was found to be large, elongated, filled with bile which could not be expressed by manual compression. The fundus of the gallbladder was bound to the hepatic flexure of the colon by adhesions. An acute angulation of approximately 60 degrees was formed between the gallbladder and its junction with the cystic duct. The common bile duct was not thickened or dilated. The gallbladder wall was thin. After freeing the gallbladder from its attachment to the colon, cholecystectomy was carried out. Histologic examination revealed mild cholecystitis.

Symptoms were relieved by the operation; the patient had remained well over a period of ten months and has regained her normal weight.

Comment

The above histories and pain descriptions are typical of true biliary dyskinesia of the hypertonic type and closely follow the pattern summarized by Westphal[1], Hill[2], Newman[3], and Ivy[4]. A hypotonic or atonic type of biliary dyskinesia has also been postulated but there is little evidence for the existence of hypotonic dyskinesia as a clinical syndrome.

The most important question which faces the clinician regarding biliary dyskinesia is the problem of diagnosis. If biliary dyskinesia is to denote a motor disturbance of gallbladder evacuation, such a disturbance should be demonstrable, both by clinical symptoms and by means of abnormal function tests. While mild disturbances in biliary kinetics have been demonstrated in a high percentage of patients undergoing special tests such as so-called serial cholecystography[5], such abnormalities are of no clinical significance unless they produce symptoms. The histories of the two cases reported here and a review of well-documented cases in the literature indicate that symptoms produced by motor disturbances of gallbladder evacuation are rather characteristic. Pains predictably follow meals, especially meals containing fat, usually by ½ to 2 hours. The pain is usually located in the right upper quadrant, is of only

moderate intensity, and is frequently associated with tenderness and occasionally with palpability of the gallbladder. Nitroglycerine frequently relieves the pain. There may be associated symptoms of nausea, vomiting, diarrhea, and flatulence but the latter symptoms are nonspecific and should not suggest biliary dyskinesia if they occur in the absence of the characteristic pain. The syndrome occurs most commonly in young women.

Routine laboratory tests usually are normal except for an occasional minimal serum bilirubin elevation such as was seen in patient A.H. Routine cholecystography demonstrates a well-filled gallbladder but evacuation is delayed or is not at all demonstrable. Depending on the type of biliary dyskinesia and the site of the obstruction, the gallbladder may not decrease in total volume after the fatty meal but may take on a globular shape ("fighting gallbladder"), and the bile ducts do not visualize; or there may be partial emptying of the gallbladder with prominent visualization and dilatation of the bile ducts; or there may be sharp angulation and kinking in the region of the infundibulum, neck or cystic duct with dye seen proximal to the angulation but none distal to it. Routine biliary drainage may show delayed emptying of the gallbladder, but this happens so often in normal individuals and the degree of normal variation is so great that the value of the test is limited.

A number of special diagnostic procedures of varying degrees of complexity have been described for the purpose of studying motor disturbances of the biliary tree. *Biliary radiomanometry* was first described by Bergeret, Caroli, and Debouvry[6] and various modifications of the original technic have been devised. In essence, these methods consist of the direct measurements of pressures in the gallbladder and biliary ducts in combination with cholangiography. Through catheters inserted into the gallbladder or biliary ducts, a radiopaque contrast solution is perfused under measured pressures. Both the resting pressures in the gallbladder and the pressures needed to overcome the resistance to perfusion of individual segments of the biliary tree are recorded. In the method of Albot et al[7], cholangiography is performed simultaneously and serially with pressure measurements. Mallet-Guy[8] performs cholangiography following the completion of pressure recordings. Both modifications require laparotomy and operative catheterization of the gallbladder and ducts. Kapandji[9] has performed biliary radiomanometry through a needle inserted into the gallbladder through the liver under local anesthesia which obviates laparotomy; this obviously poses other problems. On the basis of an extensive experience accumulated over a ten-year period, Albot and associates[7] described a series of "radiomanometric syndromes" or abnormalities of the emptying mechanism of the gallbladder as demonstrated by their technic. Their classification is too complex to be of practical clinical value, but it is noteworthy that both functional and mechanical dyskinesias due to disturbances at various levels of the biliary tree were encountered. Mechanical dyskinesias were most often caused by abnormalities in the region of the neck of the gallbladder.

A modification of biliary drainage, termed *Timed Biliary Drainage,* has been described by Varela-Lopez and associates[10]. This has also been combined with serial cholecystography[11]. Timed biliary drainage represents a refinement of ordinary biliary drainage and attempts to demonstrate a relative delay in appearance time of B-bile (gallbladder bile) and irregularity and prolongation of flow of B-bile.

Serial cholecystography described by Rose[5] is a modification of conventional cholecystography in which an attempt is made to quantitate the time relationships of gallbladder evacuation and volume changes of the gallbladder. Also, quantitative measurements of changes in position of the gallbladder during the act of evacuation are made in anteroposterior and lateral views.

All above methods have certain limitations. Serial cholecystography yields a high percentage of abnormal results and it would appear that the division between normal and abnormal results is arbitrary. Timed biliary drainage is cumbersome and the results are subject to some of the same limitations known to exist in conventional biliary drainage. Undoubtedly, the most detailed information regarding the motor function and patency of the biliary tree is obtained by means of biliary radiomanometry as described by Caroli, Albot and their associates[6,7]. This method, however, requires laparotomy which is precisely what one wishes to avoid in patients without known surgical lesions and with complaints which are possibly on a neurotic basis. The method has also been criticized because of the irritating effect of the contrast solution which may actually produce spasm not present physiologically.

The availability of highly purified cholecystokinin[12] has opened new possibilities for testing the motor function of the biliary tree. The normal response of the gallbladder to intravenous injection of cholecystokinin has been described[12,13]. Evacuation begins consistently within one or two minutes after injection and is maximal at about ten minutes. Our experience with normal individuals has been similar to the above observations. This information was utilized in the physiologic testing of gallbladder evacuation in the two patients described above. After initial conventional cholecystography, which was reported to be normal, each patient was again given 6 to 12 tablets of Telepaque. About 12 hours after the last dose, roentgen films were taken of the gallbladder area before injection of cholecystokinin and at 2- to 5-minute intervals after injection. Study of the films in both of our patients revealed marked delay and incompleteness of gallbladder evacuation, with probable acceleration of gallbladder evacuation after the administration of nitroglycerine in one patient. Both patients experienced pain similar to their usual spontaneous pain shortly after the injection of cholecystokinin.

Delayed gallbladder evacuation was confirmed by biliary drainage in which cholecystokinin was used, instead of the conventional magnesium sulfate or olive oil, to stimulate gallbladder evacuation. Again, an interval of about 10

minutes was present before dark gallbladder bile appeared in the duodenum, compared to a normal time of one or two minutes.

Judging from this admittedly limited experience with two abnormal patients and with about 20 patients with normal biliary kinetics, the method of study used by us appears relatively simple and reliable. The intravenous injection of cholecystokinin combined with modified biliary drainage and cholecystography permits accurate timing of gallbladder evacuation and detection of delayed evacuation which accompanies obstruction to the outflow of bile.

Both patients described here were operated on and found to have partial mechanical obstruction to the outflow of bile. They may be classified as having a mechanical dyskinesia in contrast to a purely functional type. Patient E. W. had a sharp kink at the infundibulo-collo-cystic junction which acted as a ball-valve mechanism permitting entry of bile into the gallbladder but preventing normal egress. Such cases have occasionally been described in the literature, notably by Schmieden[14], Berg[15], Caroli[16], and Paustian[17]. The true incidence of such cases is probably higher than suspected and the diagnosis is probably not made oftener because of the difficulties discussed. Developmental anomalies, congenital and inflammatory bands and external pressure from tumors have been said to be responsible for this type of mechanical dyskinesia. The other patient, A. H., had a very tight sphincter of Oddi in addition to numerous adhesions which compressed and obstructed the cystic duct. In both patients, the gallbladder was large, distended, and in one patient could not be emptied by manual compression. Both gallbladders showed mild inflammatory changes histologically. It is possible that prolonged stasis of bile led to gallbladder inflammation, a sequence postulated originally by Schmieden[13]. The long duration of symptoms in patient A. H. and the anatomic findings described, encourage speculation as to the course of events. It is conceivable that this patient initially had a purely functional dyskinesia due to spasm of the sphincter of Oddi. Prolonged bile stasis in the biliary ducts and the gallbladder may have led to inflammation, pericholecystitis and pericholedochitis. The latter may have produced the inflammatory adhesions which eventually bound down and constricted the cystic duct, thus superimposing a second area of obstruction.

Both patients have been followed since their operations and have remained free of their previous symptoms up to the time of this writing.

The fact that both patients described here were operated upon should not imply that surgery is necessary in the treatment of all patients with biliary dyskinesia. Treatment with nitroglycerine and diet should be tried before operative intervention is considered.

Summary and Conclusions

Two patients with mechanical biliary dyskinesia have been described. Both were young women who complained of postprandial right upper quadrant

abdominal pains of one and 10 years' duration, respectively. The pains could be relieved temporarily with nitroglycerine in one patient. Delayed and incomplete gallbladder evacuation was demonstrated by modified cholecystography and biliary drainage in which intravenous cholecystokinin was used to stimulate gallbladder evacuation. Pain was reproduced by the cholecystokinin injections.

A brief review of the pertinent literature concerning the clinical manifestations of biliary dyskinesias and the methods of their diagnosis is given. Symptoms and signs produced by impaired gallbladder evacuation are rather characteristic and usually include right upper quadrant pain, relief of the pain by nitroglycerine and palpability of the gallbladder. Biliary dyskinesia can be accurately diagnosed by special diagnostic tests once the suspicion of its existence is aroused. The syndrome should not be confused or equated with flatulence, aerophagia, or the irritable bowel syndrome.

ACKNOWLEDGEMENTS

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Cholecystokinin, prepared according to the directions of Professor Jorpes and Dr. Mutt, is presently available commercially from the Vitrum Company, Stockholm, Sweden.

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HEPATIC FAILURE AND ITS TREATMENT*

The Beneficial Effects of a High Protein Intake

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The term "hepatic failure" requires definition. Hepatic failure is not synonomous with hepatic coma. Hepatic failure, like congestive heart failure may have several stages or degrees. Hepatic coma is the advanced (or final) stage of hepatic failure. Because of the complexity of liver function, its failure cannot be as easily or precisely defined as that of heart failure.

The three distinctive cells of the liver are the parenchymal cells, the bile duct epithelium and the Kupffer cells. The Kupffer cells belong to the reticuloendothelial system and their function is similar to the corresponding cells in the spleen, bone marrow and elsewhere, and consists chiefly of phagocystosis. They may also participate in antibody formation and bile pigment formation. There is some suggestion that they may synthesize globulin[1] and therefore be be partly responsible for the hyperglobulinemia of liver disease. The chief function of the bile duct epithelium is to channel the bile from the parenchymal cells to the extrahepatic bile duct system. The bile duct epithelium may be a possible source of the increased serum alkaline phosphatase in liver disease. Complete obstruction of bile duct outflow, either mechanical, congenital, or congenital absence of intrahepatic bile ducts may cause death. Neither the Kupffer cells nor the bile duct epithelium are indispensable for the vital biochemical functions of the liver.

The functional integrity of the parenchymal cells of the liver are necessary for life. Therefore when I speak of liver failure, the reference is to parenchymal cell failure. Because these cells perform a multitude of vital functions, their failure cannot be simply defined in clinical or biochemical terms. The clinical or biochemical manifestations of failure differ in various clinical situations. Signs of hepatic failure differ in acute and chronic liver disease and in the different types of cirrhosis. Thus fever should be classified as a sign of liver failure in portal cirrhosis, but in infectious (viral) hepatitis merely a sign of the infectious process. Jaundice especially when marked and progressive is a sign of liver failure in portal cirrhosis since the jaundice as well as the fever are due to parenchymal cell necrosis and failure, while in biliary cirrhosis the jaundice depends on bile duct occlusion and does not signify failure of parenchymal cells and is compatible with long life.

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Ascites in diffuse liver disease is a sign of a failing liver and this is a poor prognostic sign. In the era (Patek and Post) before the use of high protein diets in the treatment of cirrhosis, a patient with portal cirrhosis and ascites had a life expectancy of about 6 months[2,3]. Ascites is frequently accompanied by hypoalbuminemia. Indeed hypoalbuminemia so frequently accompanies ascites that the decreased blood osmotic pressure that it engenders is thought by some[4-6] to be the major cause of ascites. While the cause of ascites is more complex and entails other factors such as increased salt retaining steroids (aldosterone), increased pituitary antidiuretic factors, and increases in portal

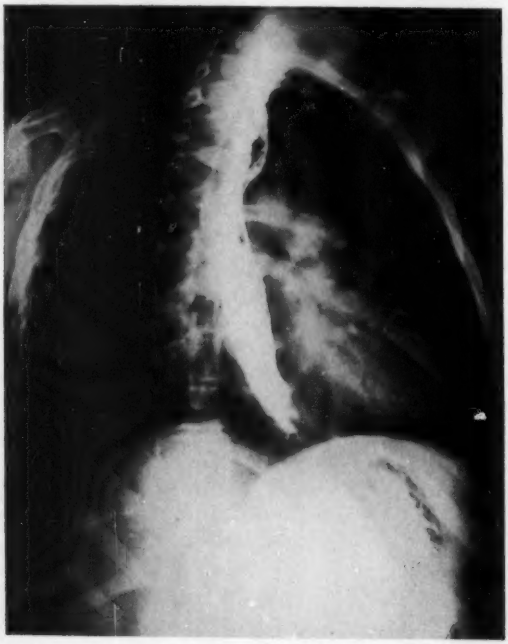


Fig. 1—Case 1, (M.G.). Esophagram showing large esophageal varices to upper third of esophagus.

vein pressure[7], hypoalbuminemia is of major importance and will be documented by the ensuing case reports. Hypoalbuminemia in itself, even in the absence of ascites is a sign of hepatocellular failure. The liver is the major site of albumin synthesis. A marked drop in the serum albumin probably also indicates that there is depletion of intracellular albumin and undoubtedly results in an interference with many cellular functions. Severe hypoalbuminemia below 2.0 gm. per cent usually signifies severe hepatocellular derangement and frequently accompanies or precedes death from hepatic failure. The fear of dietary proteins engendered

by the ammoniogenic theory of hepatic failure has intimidated many physicians in making available an adequate protein diet to patients with severe hepatic disease who are sorely in need of proteins to correct their albumin depletion. Patients with hypoalbuminemia with or without ascites can benefit from high protein diet and in some cases from intravenous serum albumin.

The following case will support the thesis of the lack of ammonia intoxication from proteins in the gut in patients with liver failure, and portocaval shunts and the favorable effect of a high protein intake plus intravenous serum albumin.

Case 1:—(M.G.) This male patient was born in May, 1943. His first admission to the hospital was in the neonatal period when a diagnosis of omphalitis was made. At the age of 1 year splenomegaly was noted. In 1952, at the age of 9, he was admitted to the hospital because of massive hematemesis. Esophageal

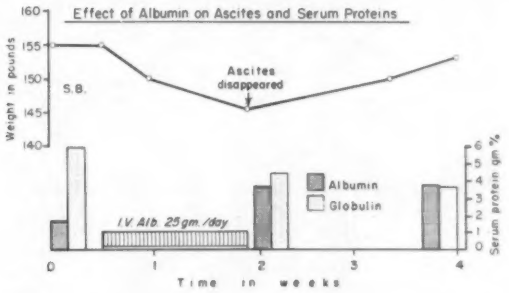


Fig. 2—Case 2, (S.T.B.). Disappearance of ascites and rise of serum albumin in a patient with postnecrotic cirrhosis treated with a high protein diet and intravenous sodium-free albumin.

varices were demonstrated and a splenectomy and splenorenal shut were performed. In 1955 at the age of 12, three years after a shunt procedure, hematemesis and melena recurred requiring esophagogastrotomy and ligation of the varices. His liver function tests remained normal, and in July of 1955 hematemesis recurred, which was stopped with esophageal tamponade. The patient was then re-explored with the view of doing a possible portacaval shunt. Portagram on the operating table showed almost complete occlusion of portal vein with a diameter of 1-2 mm.

The liver was grossly normal. No new shunt procedure was believed feasible. In 1958 he had a recurrent hemorrhage which necessitated the transfusion of one liter of blood. Esophagrams continued to show large esophageal varices (Fig. 1). This patient is now 17 years of age and has been maintained on a high protein, bland diet with antacids, and anticholinergics and remains symptom-free. He works in a photographic studio, shows no cerebral abnormalities,

no flapping tremor or *fetor hepaticus* either at present or during the bleeding episodes.

Case 2:—(A.F.) Male, age 56, developed massive hematemesis in 1956. Because of continued bleeding he had an exploratory laparotomy but the cause of hemorrhage was not evident. The bleeding stopped. On recurrent hematemesis two years later, the spleen was noted to be palpable, and a history of intemperate alcoholic consumption was elicited. Esophagoscopy revealed large esophageal varices and liver biopsy was compatible with portal cirrhosis. Liver function tests were normal with the exception of 14 per cent BSP retention at 45 minutes when the anemia was abolished by blood transfusions. At this time a portacaval shunt was attempted but because of numerous adhesions from the previous surgery and enlarged collateral intraabdominal veins this procedure

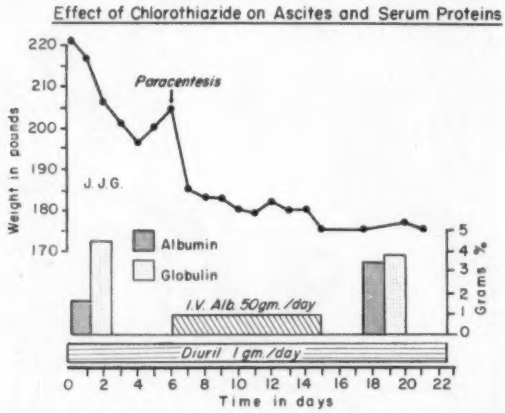


Fig. 3—Case 7, (J.J.G.). Patient with portal cirrhosis, showing disappearance of ascites and rise in serum albumin on a high protein diet and intravenous human albumin.

was surgically unfeasible and a splenectomy was done. The patient remained asymptomatic for about 18 months when he had a recurrent hematemesis requiring 1,500 c.c. of blood transfusions and a Sengstaken-Blakemore tube to stop the hemorrhage. Large esophageal varices were demonstrated by x-ray and by esophagoscopy.

His liver function tests were not abnormal at the last hemorrhage. He has remained asymptomatic on a bland diet containing over 100 gm. of protein per day, antacids and anticholinergics.

Comment:—So-called ammoniogenic encephelopathy or coma has been described in individuals with spontaneous or surgical portacaval shunts and are considered to be due to the breakdown of proteins in the gut by bacterial (urease) enzymes and the ammonia thus liberated is not carried to the liver

to be converted into urea but shunted into the general circulation. The increased blood ammonia results in cerebral dysfunction, flapping tremor and coma[8].

Neither of these two patients showed any ill effects from the massive amount of blood in the gastrointestinal tract during hemorrhage or subsequently from the high or normal protein intake. The young man (Case 1) has a complete Eck fistula since he has a complete occlusion of the portal vein and the blood from the mesenteric veins is carried to the vena cava by esophageal varices and other collaterals. In spite of a diet containing meat twice a day and no antibiotics, he never developed confusion or flapping tremor.

Patient 2 has a mild portal cirrhosis with incomplete portal vein obstruction, but massive esophageal varices which are shunting a large portion of the blood from the gut into the systemic circulation. No encephalopathy developed

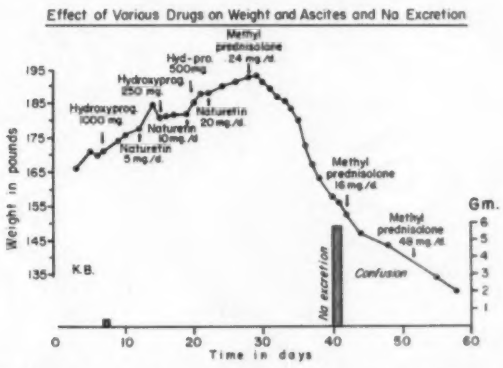


Fig. 4—Case 9, (K.B.). Patient with portal cirrhosis. Response of ascites to various drugs.

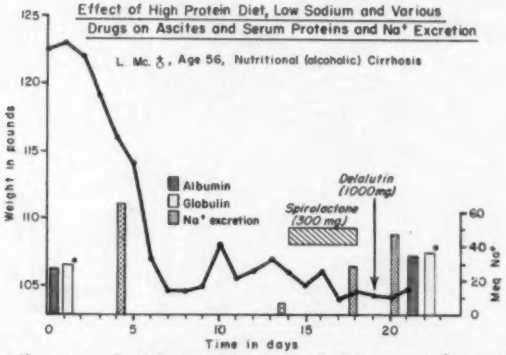
either during the hemorrhage or subsequently on a high protein intake, although he was not treated with intestinal antisepsis.

Case 3:—(A.S.) Female patient who became jaundiced at the age of 48, entered the hospital 2 February 1956. There was no history of gastrointestinal disease but light stools and dark urine were noted by patient. Physical examination revealed xantholesma, marked hepatomegaly (right lobe of liver extending to crest of ileum) and a palpable spleen. The significant laboratory findings were as follows: bilirubin was 6.5 mg. per cent; alkaline phosphatase, 54.4 u (Gomori-Kaplan modification); cholesterol, 565 mg. total; 134 mg. esterified; thymol turbidity, 6.8 u; thymol flocculation, 2+; cephalin cholesterol flocculation, 0; serum albumin, 2.7 gm. and globulin, 4.8 gm. per cent, with 1.5 alpha, 1.65 beta and 1.65 gamma fractions. Liver biopsy was compatible with a cholangiolitic biliary cirrhosis. The liver function tests with the high cholesterol which subsequently rose to over 1,000 mg. per cent, the hyperalkaline phosphatasemia, hyperbili-

rubinemia, and histologic findings placed this patient into the group of pre-xanthomatous, pericholangiolitic biliary cirrhosis with hypercholesteremia.

In October, 1958 this patient was readmitted with a severe anemia and a hemoglobin of 7.0 gm. Although x-rays of the stomach and duodenum were normal at this time, the probability is that this anemia was due to bleeding esophageal varices. Four months later, in February, 1959 the patient was readmitted with a hemoglobin of 3.5 gm., and a history of hematemesis and black stools. The patient was saved from exsanguination by a Sengstaken tube and 4.5 liters of blood transfusions. Esophagram revealed large esophageal varices.

During the hemorrhage the blood urea nitrogen rose to 35 mg. per cent. No hepatic coma developed and no flapping tremor was noted. Neomycin, 4 gm. daily was administered during the active bleeding, but this had to be discon-



*Serum albumin and globulin 2.6 gm. and 2.9 gm. at beginning of observation. This rose to 3.4 and 3.5 gm. respectively at end of observation.

Fig. 5—Case 10, (L.Mc.). Portal cirrhosis with ascites. Response of ascites and hypoalbuminemia to a high protein, low sodium diet. The effect of spirolactone and methyl progesterone on urinary sodium excretion.

tinued because it provoked marked diarrhea. The liver function tests in February, 1959, were as follows: bilirubin, 6.9 mg. per cent; alkaline phosphatase, 21 units; cholesterol, 189; esters, 84 mg.; serum albumin, 1.9 gm. and globulin 3.3 gm.

When the hemorrhage was controlled, the dietary protein was increased to 80 gm. per day. On 28 March 1959, the laboratory test showed a bilirubin of 14 mg.; alkaline phosphatase, 72.9 units; cholesterol, 569 mg.; esters 179, mg.; albumin, 2.6 gm. and globulin 3.7 gm.

On 3 April 1959, a portacaval shunt was attempted but because of the tremendous size of the liver portal vein could not be adequately exposed and a splenectomy was done. The patient recovered uneventfully from the surgery

and was discharged on an 80 gm. protein diet. Except for one recurrent bleeding episode one month postoperatively, she remains well compensated as far as the liver function goes on unrestricted protein intake plus small doses of prednisone.

Comment:—This patient has advanced biliary cirrhosis with a spontaneous portacaval shunt via the esophageal plexuses. In spite of the profuse hemorrhage with a large load of protein in the gastrointestinal tract no hepatic coma developed. This patient's liver function was impaired as evidenced by low serum albumin and elevated prothrombin time and drop of cholesterol and alkaline

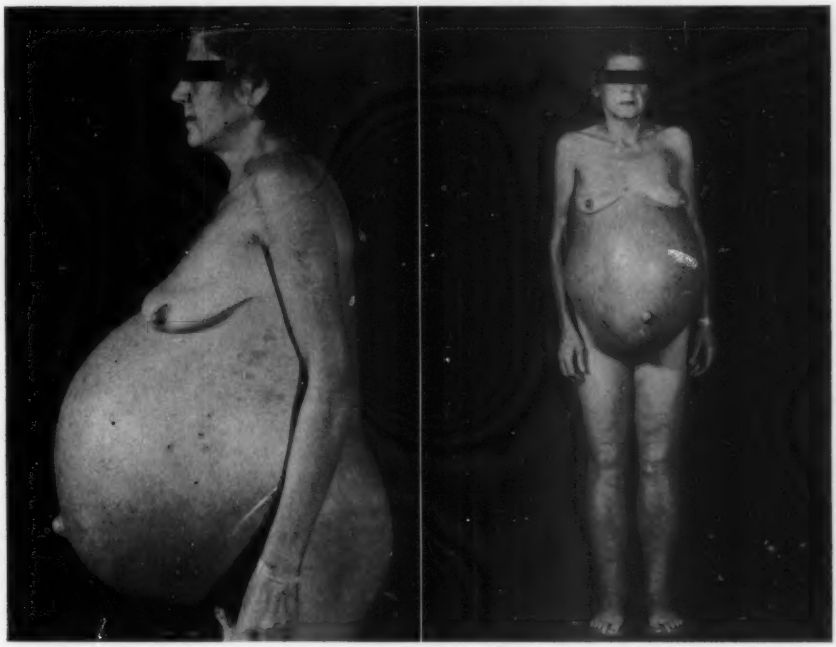


Fig. 6—Case 11, (P.V.). Massive ascites. Abdominal circumference 133 cm.

phosphatase during the hemorrhage. But in spite of intrinsic liver disease and shunting of a large portion of blood from the portal to the caval system, no ammoniogenic coma or portosystemic encephalopathy developed.

Case 4:—(L.H.) This 48-year old physician developed infectious hepatitis in 1945, while in the armed forces. He remained at bedrest for one week. In 1951 he developed epistaxis, ascites and edema. His liver function tests were abnormal and included a low serum albumin. The liver biopsy showed evidence of postnecrotic cirrhosis. He was placed on a high protein diet, which he took

when his appetite returned. The liver function tests reverted to normal, the ascites disappeared and he is clinically well at the present time, nine years after the histologic diagnosis of postnecrotic cirrhosis.

Case 5:—(S.T.B.) A 61-year old physician (born 1893) was admitted to Michael Reese Hospital in April, 1954 with a history of epistaxis, edema and ascites of 5 weeks' duration. Bloody diarrhea was present since 1953, and a diagnosis of ulcerative colitis and cirrhosis was made at a large Midwestern Clinic, about 4 weeks before. There he had paracentesis which yielded 6 liters of fluid. Mercurial diuretics were without effect.

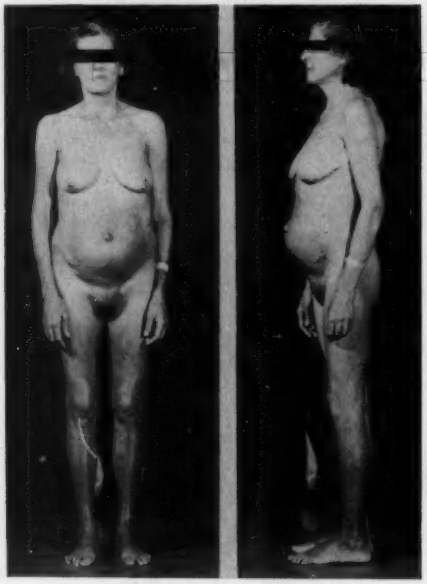


Fig. 7—Case 11, (P.V.). After therapy. Abdominal circumference 88 cm. and a loss of 102 lbs. in weight.

Physical examination revealed telangiectasias of face and upper chest, a mitral systolic murmur, marked ascites and pitting edema of legs. Sigmoidoscopic examination revealed ulcerative colitis in partial remission and three sessile polyps. About 50 c.c. of clear, amber ascitic fluid was removed for biochemical study.

The patient was treated with high protein (125 gm.) and high carbohydrate diet, Vitamin B-complex and ascorbic acid orally; sulfathalidine, 4.0 gm. a day; alpha tocopherol, 100 mg. t.i.d.; B_{12}, 60 mcg. daily intramuscularly and potassium carboresin.

He showed marked hypoalbuminemia (1.6 gm. per cent). Sodium-free human albumin, 26 gm., was administered intravenously daily. This was followed by prompt diuresis and a loss of nearly 10 pounds in weight in 10 days. The ascites has disappeared and has not recurred. The serum albumin rose and has remained elevated about 3.0 gm. per cent (Fig. 2).

Case 6:—(E.B.) Caucasian female born in 1912 was seen in February, 1959. She gave a history of drinking 6-8 bottles of beer for 8 years. During this time she was on a poor diet which was very low in protein. Complete loss of appetite occurred 6 months before and abdominal enlargement was noted recently. Patient was cachectic and had an icteric tinge of sclerae and skin. She was too feeble to walk. There were numerous telangiectasias of face and upper sternum. Numerous petechiae and ecchymoses were present over the upper arms. Abdomen was markedly distended with ascitic fluid. The liver function tests showed marked hepatic decompensation as evidenced by hypoalbuminemia, hypocholesterolemia, and prolonged prothrombin time and marked BSP retention. Upper gastrointestinal series showed no esophageal varices but the gallbladder was not visualized at this time because of poor hepatic function.

TABLE I

CASE 8, M.R. (F.) AGE 52, FATTY LIVER—PORTAL CIRRHOSIS

Date	A/G	Bil.	Alk. P.	Chol/E	BSP
11-19-56	3.6/3.2	14.7	25.5	366/79	
1-2-57	2.6/2.8	1.8	9.4	200/120	
		Ascites			39%
1-10 to 1-20	I.V. Albumin				
1-20-57	5.0/2.1	0.7	5.8 u	116/69	
2-14-57			Ascites – Parecent. I.V. Alb.		
3-14-57	3.8/3.1	0.6		358/261	8%
		Well until July, 1960			

The patient was placed on a high protein diet, containing 1 gm. sodium and supplementary vitamins. The patient's wretched appetite prevented an adequate caloric intake and glucose was given intravenously. Ascitic fluid, 8,100 c.c., was removed with a polyethylene tube. This was followed by intravenous serum albumin, 50 mg. daily for 10 days. The patient was urged and finally succeeded in consuming an adequate protein intake. The serum albumin rose from a low of 2 gm. per cent to 3.7 gm. per cent. It has remained elevated above 3.0 gm. per cent. The original weight which was less than 80 pounds, is now 113 pounds. The ascites has not recurred and the patient is asymptomatic.

Case 7:—(J.J.G.) This male patient was hospitalized at the age of 60 because of massive ascites. He gave a history of eating only one meal a day and drinking a quart of whiskey daily for many years.

Physical examination revealed mild icteric tinge of sclerae, a ruddy complexion, melanin pigmentation of skin and telangiectasias of face and upper chest. The abdomen was markedly distended with ascites, the liver and palpable 4 fingerbreadths below the costal margin, firm, not nodular nor tender. Pitting edema was present.

The diagnosis seemed obviously portal cirrhosis, and the patient was placed on a high protein, low fat diet, supplementary vitamins, chlorothiazide, 1.0 gm. daily. On this regimen the patient felt better, showed some diuresis and the edema disappeared and he lost 17 pounds in weight (Fig. 3). Because of the marked hypoalbuminemia (1.7 gm. per cent) and the persistence of the ascites, paracentesis was done with the removal of nearly 5,000 c.c. of fluid. Fifty grams of salt-free albumin was administered daily for 10 days. The serum albumin was elevated to 3.4 gm. per cent and remained elevated. The ascites did not reaccumulate (Fig. 3). The patient remained well for about 6 months when he resumed his habitual alcoholic consumption, went into hepatic coma and died in another city.

Case 8:—(M.R.) This 52-year old female entered the hospital in November, 1956, because of marked icterus. She gave a history of poor diet and consumption of inordinate amounts of alcohol for at least 4 years.

Physical examination revealed intense icterus, no spider nevi or palmar erythema. There was no *fetor hepaticus*, and no flapping tremor, but a coarse tremor of both hands was present. The liver was palpable 5 fingerbreadths below the costal margin, the spleen was likewise palpable. It will be noted (Table I) that during this stage she had marked hyperbilirubinemia and high alkaline phosphatase and elevated cholesterol but a normal serum albumin and globulin, that is a picture of cholestasis which on biopsy showed a markedly fatty liver.

A high protein diet was offered, but the patient could not eat much because of anorexia and intravenous glucose was given daily. The hyperbilirubinemia and hyperalkaline-phosphatasemia decreased (Table I) but the serum albumin dropped to 2.6 gm. and ascites developed. Paracentesis was followed by intravenous serum albumin with a rise of the serum albumin to 5.0 gm. per cent. About one month later ascites recurred, paracentesis was repeated as well as another course of serum albumin. At this time the patient was able to maintain a high protein intake. Ascites did not recur and she remained asymptomatic from the hepatic point of view till resumption of alcohol in 1960 when ascites and liver failure recurred. Her ascites at this time responded to prednisone and chlorthiazide with a loss of 17 pounds of fluid.

Comment:—These five patients have the following features in common. They all had advanced cirrhosis, (two postnecrotic and three portal); they all had hypoalbuminemia and ascites. They were all placed on a high protein diet as soon as their appetite allowed them to consume it. Intravenous human albumin was administered to all but Case 4. Case 4 was able to rid himself of the ascites with bedrest and high protein diet and his serum albumin rose to a normal level. Case 5 developed diuresis after his serum albumin was raised above 3 gm. per cent. He remained symptom-free on a high protein intake. Case 6 likewise responded to intravenous serum albumin and a high protein diet but paracentesis had to be resorted to, to rid the patient of the ascites. The ascites has not recurred and the patient has remained well.

Cases 7 and 8 both responded to intravenous human albumin and a high protein intake, but their lapse in alcohol restrictions and their return to deficient diet resulted in the serious relapses.

Case 9:—(K.B.) Negro male, age 58, with a long alcoholic history entered the hospital with marked ascites.

This man's chief problem was the ascites and this in spite of a serum albumin of 3.0 gm. per cent. His globulin was moderately elevated, 4.8 gm. The bilirubin was 7.0 mg. per cent. His appetite was good and he consumed an unrestricted amount of protein, over 100 gm. a day. He also had large esophageal varices demonstrated roentgenographically and esophagoscopically.

As will be seen from Figure 4, his ascites did not respond to hydroxy-progesterone with and without naturetin. On 24 mg. methylprednisolone and 20 mg. naturetin daily, there was a marked diuresis. The sodium excretion rose from 5 mg. in 24 hours to 5.9 gm. (Fig. 4).

Shortly after the methylprednisolone was reduced (Fig. 4), he developed mild confusion without apparent electrolyte imbalance. The medical resident promptly reduced his protein intake but at the same time increased the methylprednisolone to 48 mg. daily and the cerebral symptoms subsided promptly.

Case 10:—(L.Mc.) This 56-year old female patient was admitted to The Research and Educational Hospitals because of abdominal enlargement of 4 weeks' duration. Two months before admission she developed anorexia and emesis. For 8 years she ingested about 1 liter of whiskey per week in addition to beer. She has been on a grossly poor diet especially as regards protein containing foods. Physical examination revealed a jaundiced patient with poor skin turgor. A spider nevus was noted on her left arm. Telangiectasis of face and chest were present. Marked ascites and pretibial edema were present. Neither the liver nor the spleen could be palpated because of the ascites. Liver biopsy revealed portal cirrhosis. She was placed on bed rest and high protein diet, with 200 mg. of sodium per day with good diuresis (Fig. 5). The patient tolerated the high protein diet well and the serum albumin rose from 2.6 to 3.4 gm.

The cholesterol level rose from 125 mg. to 262 and the prothrombin rose from 45 per cent to 90 per cent. Sodium diuresis of 64 mEq. per day was obtained on the high protein diet and sodium restriction alone. This decreased to 6 mEq. Spirolactone caused an increase to 27.8 mEq. and subsequently (delalutin) hydroxyprogesterone 1,000 mg. intramuscularly caused a further increase to 46 mEq. per day. The serum sodium remained normal.

Case 11:—(P.V.) This 43-year old female patient was admitted to the Illinois Research Hospital for the first time in 1959 when a diagnosis of portal cirrhosis with esophageal varices was made. She then had minimal ascites. She resumed her customary excessive, alcoholic intake, discarded the low sodium diet, and was re-hospitalized in February, 1960, because of dyspnea, marked abdominal enlargement and swelling of legs.

Physical examination revealed moderate icterus, massive ascites (Fig. 6) with umbilical hernia, marked edema of lower extremities all the way to the inguinal region and telangiectasis of face.

She was treated with a high protein diet, containing 500 mg. sodium, hydrochlorothiazide, 50 mg. daily and spirolactone, 400 mg. per day. Marked and steady diuresis ensued, she lost over 100 pounds in weight (Fig. 7). She showed a good sodium diuresis, rising from 67 mEq. per 24 hours 3 days after institution of therapy, to 301 mEq. one week later. Her potassium excretion was 108 mEq. per 24 hours. BSP retention was 46 per cent initially; after 3 weeks it had decreased to 24 per cent.

After two months of diuresis and high protein therapy, mild lethargy and confusion occurred and the house physician promptly reduced her protein intake but it was also noted that the serum potassium was below 3 mEq. No flapping tremor developed. A depression and suicidal episode developed subsequently which was probably independent of hepatic toxemia.

Comment:—All these three patients had massive ascites due to severe, advanced portal cirrhosis. Case 10 responded to bedrest and a high protein, low sodium intake. Sodium diuresis occurred on this regime. The sodium diuresis lagged and was increased by spirolactone and further by hydroxyprogesterone (delalutin) (Fig. 5).

The ascites in Cases 9 and 11 remained unchanged in spite of bedrest and a high protein diet, low in sodium, but it did respond when other drugs were added. Case 9 responded well to a combination of methylprednisolone and naturein. Case 11 responded to hydrochlorthiazide and spirolactone with a loss of over 100 pounds (Figs. 6 and 7).

Toward the end of the diuresis both patients developed some cerebral symptoms. This, however, cannot be attributed to the high protein intake, as they were on a high protein intake throughout this period of therapy, (for over 30 days in Case 11) and the cerebral manifestations occurred after marked diuresis.

Patient 11 also showed hypokalemia, and marked depression compatible with the personality of an alcoholic. Patient 9 improved when the protein intake was decreased but the methyl prednisolone which was previously decreased, was raised when the cerebral manifestations were noted. Steroid hormones have a favorable effect on hepatic coma and their abrupt reduction in patients with liver disease may result in hepatic coma[9].

Comment

Hepatocellular failure in chronic diffuse liver disease such as cirrhosis is invariably accompanied by hypoalbuminemia, which is frequently accompanied by ascites. Many of these patients show other evidence of protein malnutrition such as poor skin turgor and marked decrease of muscle tone and volume. Several decades ago much experimental evidence appeared: 1. Implicating protein deficiency and especially the deficiency of sulfur-containing amino acids in the production of hepatic necrosis[10-13]; 2. Indicating the injurious effects of excessive fats and deficiency of proteins in maintaining the integrity of the liver[14-18]; and 3. The role of protein in protecting it against noxious agents[19-21].

Currently there was a report in the literature indicating that proteins protect rats against the virus of experimental hepatitis[22]. High protein diets have been utilized since the demonstration of their usefulness by Patek and Post[2,3]. My observations in the cases discussed indicate that high protein intake, if acceptable to the patient with supplementation by intravenous albumin, is still an acceptable and successful form of therapy. The implication of proteins in the production of hepatic coma or ammoniogenic encephalopathy had its inception in the experimental work of Hahn[23] and Balo and Korpassy[24]. The recent literature is replete with papers dealing with the supposed toxicity of ammonia arising from the gastrointestinal tract which is not converted to urea by the malfunctioning liver. The first three patients had large esophageal varices (Eck fistulas) which shunt blood from the gut to the systemic circulation, two of these with liver diseases, and yet no ammoniogenic coma developed as observed by McDermott[25].

The development of cerebral manifestations in two patients after marked diuresis cannot be attributed unequivocally to the high protein intake. The tapping of ascites may be followed by coma and these patients have lost much ascitic fluid. The rapid decrease of steroids in one patient has been mentioned, as a possible factor in the production of cerebral symptoms. The usefulness of raising the serum albumin in the treatment of ascites was demonstrated in several of our cases. The need of an adequate protein intake to maintain a normal serum albumin level should be axiomatic.

The reversal of sodium retention by the chlorothiazide drugs can be aided by an antialdosterone such as spiraloctone. Hydroxyprogesterone (delalutin) may likewise have antialdosterone properties[26]. In one of our cases it caused an

increase in sodium excretion, in the other one it apparently failed. The combination of a thiazide and steroid is also effective (Case 9). Indeed it is possible that glucosteroids may in some way inhibit the liberation of aldosterone.

The danger of the thiazide diuretics is not in increasing blood ammonia as was originally thought, but in electrolyte (potassium) depletion. The aldosterone antagonists should theoretically cause potassium retention and neutralize the potassium loss from the thiazides. The steroids may likewise enhance potassium loss and even patients with untreated liver failure may cause negative potassium balance. Therefore, administration of supplementary potassium in 3 to 6 gm. daily or more is imperative in the treatment of liver failure with water and sodium retention.

Summary and Conclusions

1. Hepatic failure prior to the development of hepatic coma is accompanied by marked hypoalbuminemia, which in turn is a factor in water retention and ascites formation.

2. Administration of a high protein diet to such patients supplemented, when necessary, with intravenous albumin is therapeutically sound and frequently effective.

3. Three patients with spontaneous portacaval shunts are tolerating a high protein diet without any cerebral dysfunction.

4. The judicious use of low sodium intake, thiazide drugs, antialdosterone drugs, and prednisone are effective measures in the treatment of ascites due to liver failure.

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TREATMENT OF HEPATIC EDEMA*

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The sodium and water retention associated with advanced liver disease is influenced by many physiopathologic factors. The complexity of the pathogenesis of edema of hepatic origin still denies investigators a complete understanding of all the pathologic features of the primary liver disease itself as well as the compensatory factors that are involved in this syndrome. The multiplicity of influences such as portal hemodynamic changes, shifts and decrease in colloid osmotic pressure, decreased destruction and possibly increased production of salt retaining hormones, renal factors, and antidiuretic hormone and capillary permeability are all integrated to produce an edematous state that frequently presents the greatest problems in therapy.

Edema due to liver disease usually infers a significant degree of hepatic parenchymal failure. Therefore, the therapy of hepatic edema demands a dual approach. On the one hand, the general measures necessary for improving hepatocellular function are mandatory for reversing the basic mechanisms of the physiopathology of the edema. On the other hand, the more specific measures used to produce a negative sodium and water balance have no direct influence on the basic disease process. The edema may respond to the more specific measures but the hepatocellular disease may deteriorate. Therefore, an integrated approach of both the general and specific measures appears to be the rational therapeutic regimen for hepatic edema. In Table I the general and specific measures in the approach to the therapy of hepatic edema are summarized.

General Measures

The general nutritional and supportive measures routinely used are directed toward the therapy of the liver disease itself rather than the reduction of excess sodium and water retention. The type and degree of liver disease that is present influences to some extent the response of the fluid retention to these general supportive measures. The response of the ascites and edema in the patient with fatty infiltration and cirrhosis of the liver might be more gratifying with a well balanced diet and general supportive measures than in the patient with severe postnecrotic scarring of the liver.

The role of dietary protein in the therapy of hepatic disease has been difficult to evaluate but there is much evidence to point to the benefits of high

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protein intake on the ultimate course of hepatic disease. A well balanced diet with adequate fat for palatability is a cornerstone in the direct therapy of the liver disease itself. The quantity of protein in the diet will, out of necessity, be influenced by the degree of hepatic encephalopathy resulting from the protein ingestion. Ammonia intoxication may become a primary factor in influencing the quantity of protein that is allowed in the diet and a titration of dietary protein may be necessary in order to determine the maximum amount of protein that can be used without producing encephalopathic symptoms.

The necessity for abstinence from alcohol is obvious. Multivitamin and yeast therapy for the associated deficiencies found in the chronic alcoholic

TABLE I

TREATMENT OF HEPATIC EDEMA

General Measures:

A. Rest—strict—supine
B. Dietary (adequate protein, carbohydrate and fat)
C. Multivitamin therapy
D. Therapy of concomitant illness (infection, anemia, etc.)
E. Abstinence from alcohol

Specific Measures:

A. Sodium restriction (500 mg. of sodium or less)
B. Diuretic therapy
   1. Mercurials
   2. Phthalimidines
   3. Thiazides
   4. Combination of diuretics (potentiated by acidifying agents and and aminophylline)
C. Antialdosterone agents with diuretics
D. Adrenal steroids with diuretics
E. Osmotic agents (salt-poor albumin)
F. Paracentesis (only when ascites produces a marked mechanical problem or to help initiate a diuresis)
G. Portacaval shunt (after prolonged medical failure and adequate hepatocellular function)

with malnutrition and cirrhosis is mandatory and the use of parenteral thiamine chloride in the patient with associated beri beri is indicated.

The use of forced rest in order to decrease stress on the liver cell becomes a necessity in hepatic disease with edema. Simultaneous improvements in renal blood flow and renal function may also occur and benefit the patient who maintains bed rest. The use of the supine position in order to help mobilize peripheral fluid and favorably influence renal blood flow is indicated in those cases that are refractory to routine therapy.

Paracentesis presents a hazard to the general condition of the patient and may be the trigger mechanism for precipitating hepatic coma. The loss of protein and electrolytes with overzealous paracentesis will usually be harmful and the loss of abdominal fluid by this method is followed by rapid reaccumulation of the ascites. The indication for paracentesis is primarily mechanical and should be done when the abdominal distention becomes severe enough to produce troublesome physical respiratory distress in the patient. Severe ascites may increase abdominal pressure to the point of inhibiting venous and lymphatic drainage from the legs. This may increase peripheral edema and possibly decrease renal blood flow. In this case the removal of small quantities of ascitic fluid may result in a diuresis and improvement in the patient's response to diuretic and other measures.

TABLE II

EXCRETION OF SODIUM AND POTASSIUM AS MEQ./24 HOURS BY CIRRHOTIC PATIENTS GIVEN 1,000 MG. OF CHLOROTHIAZIDE DAILY

Pts	Na		K		ND
	C	AR	C	AR	
1	5	9	45	50	3
2	5.2	10	22	69	6
3	40	27	30	10	5
4	51	77	12	14	4
5	125	63	50	21	3

C: Control excretion
AR: Average daily response above control levels
ND: Number of days observed

The aggressive treatment of intercurrent infections which notoriously may precipitate decompensation of liver function in the patient with chronic hepatic disease must be instituted. Pulmonary infection in the patient with massive ascites and restricted diaphragmatic movement is a real hazard and must be guarded against. Anemia due to a multiplicity of causes such as nutritional, blood loss and hypersplenism should be treated as efficiently as possible. Adequate blood replacement will improve hepatic and renal function with favorable effects on the diuretic response.

The use of portacaval shunt as a surgical procedure for therapy of ascites is still in an experimental stage and controversial. It should be done in the rarest occasions only after the patient has had an unsuccessful response to adequate medical care. The patience of the physician and patient for at least a year would appear indicated. If ascites is still a problem of a psychological

or a mechanical nature and the patient's hepatocellular function puts him in a good risk category then portacaval shunt may be considered. The presence of esophageal varices would add a further indication for surgery at this time.

Specific Measures

Sodium restriction in liver failure with edema is obviously indicated since the marked positive sodium balance found in this syndrome must be influenced by regulating sodium intake and attempting to influence its output. The use of a palatable diet with 500 mg. of sodium or less with balanced nutritional components can be accomplished by adequate instruction to the patient about those high sodium foods that must be avoided and by the intelligent selection of the varied low sodium foods available. The degree of adherence to a low sodium diet that can be maintained by the patient depends upon his socioeconomic

TABLE III

Urinary Sodium and Potassium Excretion as mEq./24 Hours by One Cirrhotic Patient Given Mercurial and Thiazide Diuretic Therapy

	Mercurial (2 c.c.)		Hydrochlorothiazide (100 mg.)	
Day	Na	K	Na	K
C	55	28	0.5	5
1	100	35	1.0	5
2	75	52	1.5	15
3	160	43	2.5	25
4	100	48	20	40

status, intelligence and desire to get well. The use of condiments, flavorings, fats and oils to improve the palatability and desirability of the diet becomes necessary to maintain the patients interest in his food.

The tolerance to salt of the cirrhotic patient on marked sodium restriction varies over a wide spectrum. The 24-hour urine sodium excretion gives some predictability of the response to diuretic agents. In Table II the 24-hour urine sodium and potassium excretions are shown in five cirrhotic patients. The control sodium excretion of the first two patients is significantly low (5 mEq.) with a noticeably larger potassium excretion. The change in sodium excretion to 1,000 mg. of chlorothiazide daily in these patients is insignificant as compared to the responses seen in patients 4 and 5 who are at the other end of the spectrum where control sodium excretion is high showing a negative sodium balance while on a low sodium intake. Patients 4 and 5 have a significant increase in sodium

excretion with the diuretic. Another interesting aspect is the noticeably higher control potassium and its response to the diuretic in patients 1 and 2 inferring the possibility of significant secondary aldosteronism in these patients. Therefore, the general status of the patient's physiopathology will significantly influence the response to diuretic agents as well as the inherent pharmacololgic attributes of the drug itself. In Table III the 24-hour urinary sodium and potassium excretion is shown in one patient during two phases of his illness. In the first phase the patient's control sodium excretion was 55 mEq. and the response to mercurial therapy was quite adequate. In the second phase of this study the patient's condition deteriorated quite significantly and his control sodium excretion dropped to 0.5 mEq. The response to 100 mg. of hydrochlorothiazide daily

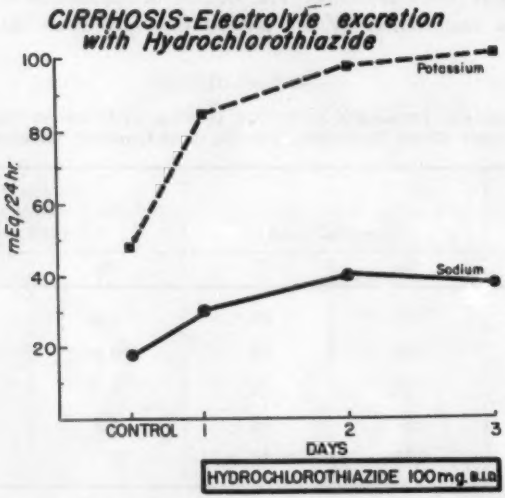

Fig. 1—The 24-hour urine sodium and potassium excretion in a cirrhotic patient given 200 mg. of hydrochlorothiazide. There is little effect on sodium excretion but a significant increase in potassium excretion is noted.

was insignificant in this phase of the patient's illness. Therefore, the response to the diuretic agents in this case was influenced by the degree of aberration of the patient's physiopathology. It is likely that the hydrochlorothiazide would have had as significant an effect as the mercurial, had it been used in the first phase of this study.

The use of diuretics and sodium restriction is the cornerstone of the specific therapy of hepatic edema. The parenteral mercurial diuretics still remain the most potent available diuretic agents and their use is indicated when general measures and sodium restrictions are not sufficient for the adequate reduction in edema. The oral mercurials are relatively inadequate in their effects as com-

pared to the parenteral mercurials. The dose of the parenteral mercurial is usually 2 c.c. daily but occasionally doses of 3 and 4 c.c. may be necessary to achieve diuresis. When there is a poor response to one mercurial then usually other merucurials are also inadequate. The attempt, however, at using another drug is occasionally sucessful. To potentiate the effects of the mercurials and

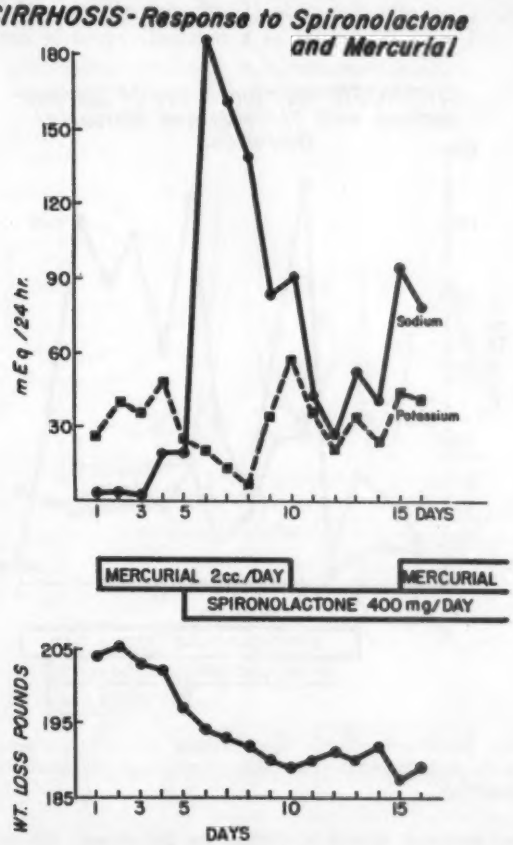

Fig. 2—Sodium and potassium excretion in a cirrhotic patient given spironolactone and mercurial therapy alone and combined. Increased sodium results only with the combined therapy.

other diuretics the use of aminophylline intravenously preceding the drug may produce additive effects. Another method of potentiating the mercurial response is by producing an acidosis by the use of acidifying agents such as ammonium chloride, calcium chloride and the mono hydrochloride of certain amino acids.

The use of an ammonium salt obviously has inherent danger in the possible production of ammonia intoxication in the hepatic patient and should be used cautiously. Ten to 20 c.c. of a 25 per cent solution of calcium chloride given four times daily will help produce a hyperchloremic acidosis which has significant influence on the mercurial diuresis. Usually three to five days are necessary to obtain an adequate acidosis. The use of the carbonic anhydrase inhibitors as acetazolamide (Diamox) or ethoxzolamide (Cardrase) will potentiate the acidifying effects of the acid salts. Their use as a naturetic agent is not primarily indi-

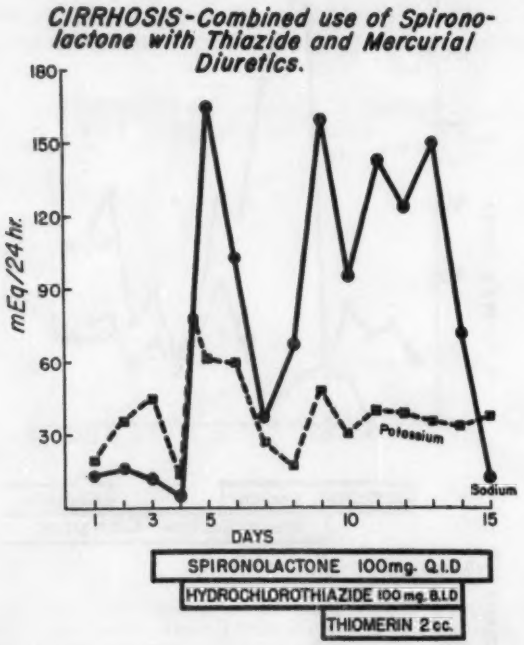

Fig. 3—Sodium and potassium excretion in a cirrhotic patient given spironolactone, hydrochlorothiazide and thiomerin. The additive effects of the combined diuretic therapy are demonstrated.

cated since they are not nearly as potent as the mercurials or thiazides. The carbonic anhydrase inhibitors will produce significant bicarbonate and potassium excretion with a resultant metabolic imbalance, and also increase blood ammonia levels. Close observation for hepatic encephelopathic symptoms must be maintained during their use.

The thiazide diuretics are quite potent agents and have the additional advantage of oral administration. The maximum effective dose of these drugs should be used to insure adequate response. Lower maintenance doses may be

prescribed when stable weight and a "dry" state is attained. The maximum effective dose of chlorothiazide (Diuril) is 2,000 mg. and that of hydrochlorothiazide (Hydrodiuril, Esidrix, Oretic) is 200 mg. The lower dose range thiazide diuretics such as benzydroflumethiazide (Naturetin,) trichlormethiazide (Naqua) have a maximum effective dose of 10 mg.

The phthalimidine diuretic agent available (Hygroton) has a maximum effective dose of 200 mg. The three major groups of diuretics mentioned have

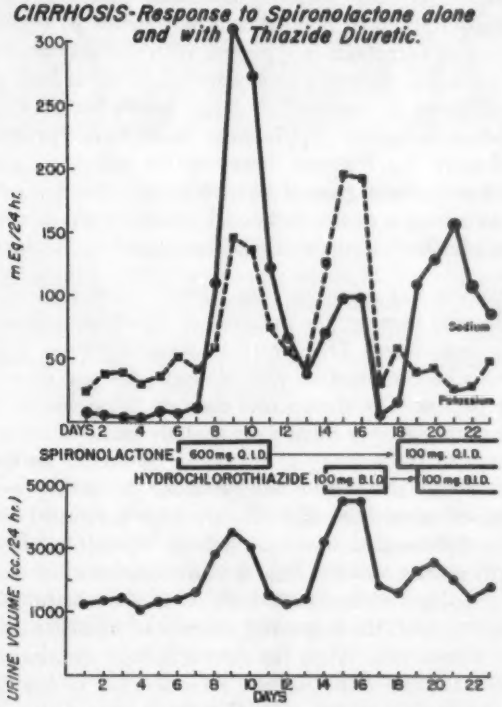

Fig. 4—The response to high doses of spironolactone in this patient appears to be pharmacologic since this is an increase in both sodium and potassium excretion. When spironolactone is administered in therapeutic doses with hydrochlorothiazide there is an increase in sodium excretion and potassium excretion is minimally effected.

similar as well as individual modes of action and frequently their combined use is additive and beneficial when one drug is not adequate for producing the desired diuresis.

The use of salt-poor albumin as an agent for increasing oncotic pressures is helpful but the expense and the necessity for large quantities creates a disadvantage. Not uncommonly at least ten 25-gram units are necessary before a

significant response to diuretic agents is realized. When routine diuretic measures have failed the use of salt poor albumin is certainly indicated and should be given in adequate volume when possible.

When diuretic agents are used on a continuous basis the poor response to the agent as measured by weight loss and urine volume may give the physician a false sense of security that no effects are being produced. In cases, however, where there is a low sodium excretion and possibly secondary aldosteronism is prevalent, diuretic therapy may increase potassium excretion to significantly high levels and the complications of hypolalemia may result. In Figure 1 the 24-hour sodium and potassium excretions in a patient with cirrhosis treated with 200 mg. of hydrochloromethiazide daily are demonstrated. There is little effect on sodium excretion but potassium is excreted in large quantities. If this were allowed to continue indefinitely severe hypokalemia could have resulted. This demonstrates very definitely the frequent necessity for adequate potassium supplements in the cirrhotic patient given diuretic therapy. The frequent determination of the blood urea nitrogen is also indicated with chronic diuretic therapy as a quick evaluation of other electrolyte imbalances such as sodium depletion, etc.

When the patient has a low sodium excretion and a poor response to salt restriction and diuretic therapy, the presence of significant secondary aldosterone effects should be considered. The use of an antialdosterone agent (spironolactone) as Aldactone in combination with diuretic therapy should be attempted in the refractory patient. The therapeutic dose of Aldactone is 100-200 mg. four times daily. It may take two or three days of daily administration before there is significant response to the activity of this drug. It should be used in combination with the diuretics since its influence alone is usually not of significant degree to produce effective diuresis. In Figure 2 the combined use of a mercurial diuretic with the spironolactone in a cirrhotic patient is demonstrated. The response to the mercurial alone before the administration of the spironolactone is negligible and sodium excretion is low. After the combined administration of the spironolactone with the mercurial there was significant sodium excretion with an effective weight loss. When the mercurial was withdrawn and aldactone was continued the 24-hour urine sodium excretion fell to low levels but again increased upon resumption of mercurial therapy.

In Figure 3 the combined effects of the spironolactone and two diuretic agents is demonstrated. The combined use of the spironolactone and hydrochlorothiazide is quite effective but by the seventh and eighth days there is a significant fall in sodium excretion. The addition of 2 c.c. of thiomerin on the ninth day increased the sodium excretion again to higher levels. When both the mercurial and thiazide are stopped the sodium excretion fell quite precipitously although the spironolactone administration was continued.

In Figure 4 a large dose of the spironolactone (600 mg. four times daily) was given to a cirrhotic patient. A large potassium as well as sodium excretion

resulted. This demonstrates a possible pharmacological effect of the drug on the renal tubule at the high dose level rather than an antialdosterone effect in fact of the significant increase in potassium excretion. When 200 mg. of hydrochlorothiazide was administered a significant increase in potassium excretion above that of sodium resulted similar to that seen in Figure 1. This type of response may well demonstrate the case where secondary adosterone effects are influential. This appears to be borne out by the response seen in this patient when the combined use of 200 mg. of hydrochlorothiazide with a therapeutic dose of the spironolactone (100 mg. four times a day) are administered. With this combination of drugs there is again a significant sodium excretion but now the potassium loss is not significantly influenced. This demonstrates the desired action of the combined use of the spironolactone with a diuretic agent in which sodium excretion is accentuated and the increase in potassium excretion is kept at a safe level.

The combined use of adrenal cortical steroids with diuretic agents has been recommended for use in initiating a diuresis when other measures have failed. This combination is unpredictable and may result in increased sodium retention. The attempted use of the adrenal steroids in the absence of response to other measures should be considered, especially when a dilutional hyponatremia is present. The addition of the adrenocortical steroids may influence glomerular filtration and tubular reabsorptive mechanism in such a manner as to initiate a significant diuretic and saluretic response.

Summary

Rest, sodium restriction, dietary measures and diuretic therapy are frequently adequate in controlling mild hepatic edema. In the more severe cases the use of colloid therapy and paracentesis may help initiate a diuresis. Refractory cases may be favorably influenced by antialdosterone agents and adrenal cortical steroids in combination with diuretics. Portacaval shunt is limited to the good risk patient who has had a prolonged medical failure.

Discussion

Dr. Julian A. Sterling (Philadelphia, Pa.): It is gratifying indeed to know that the essayists this morning have given you more than just a superficial view of a problem which we could take one month to discuss night and day in all detail. They have given you, in my opinion, a very superior interpretation of a very important problem. I think that Dr. Fuchs, Dr. Spellberg, Dr. Goldstein and their coworkers are to be congratulated on their succinct presentations.

I would like to comment briefly on some of the material that has been presented. You recall that Dr. Goldstein stated that there are extrabiliary tract and intrabiliary tract causes for pain or the syndrome that he has described as "dyskinesia". He has further amplified it for you to indicate that there may

be a hypotonic or a hypertonic dyskinesia. Please interpret these properly for yourself. The pain of hypotonic dyskinesia is that due to sluggishness in flow where there is insufficient pressure in the biliary tract to overcome the sphincter mechanisms. It is undecided in many circles as to whether the hypotonicity is secondary to spasm at the sphincter or whether there is an inadequacy of the emptying mechanism of the biliary tract. The hypertonic dyskinesia occurs where some obstacle exists to emptying of the biliary tract, and in these situations the choledochal, cholecystic and intrahepatic duct pressures are exquisitely high.

For many years we have been investigating the pressures within the duct systems. We know that when the duct system pressures get over 35 cm. of water (or of bile) that the hepatic cell may then cease to function.

Further, at operation it is extremely important when you have the problem of biliary dyskinesia confronting you, that you exclude organic disease which can produce abnormalities in the pressure systems in the biliary duct. It is very important to establish positive diagnoses. Organic disease may be missed. So-called fibrosis or spasm of the sphincter of Oddi may or may not exist. As a principle, I will always do a cholecystocholangiogram at the operating table in such doubtful cases to identify the presence or absence of organic disease.

It has been previously considered that dyskinesia is a waste basket diagnosis. This is not true. As Dr. Goldstein and his coworkers indicated to you, there are specific features upon which you can pin the diagnosis of dyskinesia, keeping in mind that hypotonicity or low pressure is one phase and that hypertonicity or high pressure is the other phase. It is important to exclude the presence of organic disease.

Now, do not confuse biliary dyskinesia with the so-called postcholecystectomy syndrome. The postcholecystectomy syndrome is definitely a waste basket category. In this we have errors of misdiagnosis, psychiatric problems, traumatic problems reference to the surgery, errors in original diagnosis where the cause for disease was not in the biliary tract, as well as those which may represent dyskinesia of the hypertonic or hypotonic varieties. So be very cautious in indicating a specific syndrome postoperatively as being dyskinesia. Be alert, however, as Dr. Goldstein has indicated, to the fact that you can have functional disease in the biliary tract. This functional disease may be identified and should be identified, but it is tremendously important to identify organic disease when it exists.

I would like to comment with reference to Dr. Spellberg's paper. Up to now we had been avoiding blood, protein, albumin, etc., in the therapy of individuals with hepatic insufficiency because of the fear that hepatic coma will result from the inefficient metabolism of the amines, which are the end products of protein digestion. Dr. Spellberg has indicated the circumstances un-

der which high protein therapy is effective. I would like to emphasize that the diagnosis of hypoalbuminemia, including a reversal of the A/G ratio, is a significant, positive and absolute indication for the feeding of albumin to patients with hepatic disease. We recommend, for example, in our babies with cirrhosis that we give 16 to 20 egg whites daily. If they can take them, they are extremely benefited. This, supplemented by corticoids and other medications, is of extreme value. But the indication for the protein therapy must depend on the determination of the serum protein. Some patients, however, may not tolerate, metabolize or use the proteins adequately.

I want to caution you against a concept and perhaps Dr. Spellberg will say I am wrong. Take the individual who has an elevated serum bilirubin which may be due to cholestasis and this serum bilirubin then begins to decrease and you say this patient is better. Be cautious about that statement of improvement. One of the first signs in hepatic failure, earlier than reversed A/G ratio, is the fact that the liver cell loses its ability to convert the bilirubin to the pigment which you can measure. You must have other evidences of improvement, other than the change in level of serum bilirubin which, in itself, is variable. I, therefore, would like to comment on one of his statements: that the "serum albumin decreased in spite of the fact that the serum bilirubin appeared to decrease"—a sign of improvement. I do not think that decrease of serum bilirubin is adequately substantiated as a sign of improvement. It must be particularly borne in mind in patients who have obstructive jaundice that when their serum bilirubin drops you do not assume that this patient is well or getting better, unless you have positive evidence that sufficient bile is entering the intestinal tract. Be cautious about that. A drop in serum bilirubin can be an early sign of hepatic failure.

That is all I would like to comment upon at this moment. Perhaps Dr. Wirts would comment further and perhaps if he has time he can ask the discussants many of the questions that you have asked.

Dr. C. Wilmer Wirts (Philadelphia, Pa.):—The first question dealing with the presentation by Dr. Goldstein is: Describe the x-ray changes of the cholecystogram after intravenous cholecystokinin in normal persons.

Dr. Franz Goldstein (Philadelphia, Pa.):—In normal persons there is a very rapid decrease in gallbladder size. The gallbladder contracts within a couple of minutes. The smallest size is usually attained in about 10 minutes and then gradually the gallbladder starts filling up again. In our cases, there was never any great decrease in size; we estimate that the gallbladder decreased about 30 per cent in size. It also took on this globular appearance which suggests that the gallbladder is fighting to overcome resistance.

Dr. Wirts:—How do you account for the fact that people who have cholecystectomy for gallbladder disease often present themselves with biliary dys-

kinesia postoperatively and how do you treat them? I think Dr. Sterling touched on that.

Dr. Goldstein:—I think Dr. Sterling has already answered that question. I think in most such cases there is an error in diagnosis. Many physicians are still under the impression that if a patient belches and has gallstones, the gallstones are the cause of the belching. There is no indication that gallstones have anything to do with belching or certain other nonspecific gastrointestinal symptoms. If a gallbladder in the absence of a history of biliary colic or local signs of inflammation is removed, it is removed for prophylactic purposes to prevent further disease, and one should not expect that the belching will stop. In most instances of "postcholecystectomy dyskinesia" the patient continues to have his irritable bowel syndrome or aerophagia which he had before the operation. We do not think that this is dyskinesia.

Dr. Wirts:—Where is the purified cholecystokinin obtainable for clinical use?

Dr. Goldstein:—There are two sources at present. We have obtained ours from Sweden. It was originally provided, to Dr. Wirts, through Professor Jorpes in Stockholm. It is now manufactured by the Vitrum Company in Stockholm. I think an ampule costs $3.00. Another preparation is made by the Boots Company in Nottingham, England, at about $5.00 an ampule. We have only used the Swedish preparation and have had no adverse effects other than a little flushing of the face which is to be expected.

Dr. Wirts:—What is the dose of intravenous cholecystokinin for stimulation?

Dr. Goldstein:—The dose is one unit per kilogram. The ampules contain 70 i.v. units. It is safe to inject a whole ampule, or one can use less in a smaller person, based on weight.

Dr. Wirts:—Are there any true proven cases of biliary dyskinesia with no anatomical pathology?

Dr. Goldstein:—Yes; the initial cases described were supposed to be due to purely functional disturbances. Our cases were actually falling into the category of mechanical dyskinesia; there were mechanical obstructive factors present. The symptoms are indistinguishable. In the first patient we described, we thought there may have been a combination of functional and mechanical factors present. Perhaps the initial thing was spasm of the sphincter of Oddi, later on followed by inflammatory changes and adhesions which bound down the cystic duct.

I do not think that functional dyskinesia is a very common condition; most cases which have been well documented have been of the mechanical type.

Dr. Wirts:—It says here, "Biliary dyskinesia is a rather shaky diagnosis on which to advise surgery. Will lack of drainage with ordinary fat meals suggest

the diagnosis and what findings on ordinary cholecystogram will suggest the cholecystokinin test?"

Dr. Goldstein:—I agree that this is a very difficult diagnosis to make by ordinary means. I think that is the reason why patients either have not been diagnosed who actually had this illness or the diagnosis has been used as a waste basket diagnosis, as Dr. Sterling said. The diagnosis can be made by tests as we described, putting on a quantitative basis the time relationship of gallbladder emptying and of the cholecystographic changes. The other tests which I mentioned are also helpful but they are time-consuming and they are really not very practical. We hope that with the present availability of cholecystokinin there will be more objective demonstration of impaired gallbladder emptying, which is exactly what biliary dyskinesia means. The tests should be performed in patients whose history suggests dyskinesia and whose gallbladder fails to empty after a fatty meal.

Dr. Wirts:—Thank you, Dr. Goldstein. I would like to present some questions to Dr. Spellberg and the first one is: "At what point does the level of protein intake give difficulty in: 1. normal livers, 2. livers with embarrassed function, or impaired function?" Dr. Spellberg.

Dr. Mitchell A. Spellberg (Chicago, Ill.):—I think normal livers can take an indefinite amount of protein. Of course, a pure protein diet in human nutrition would hardly be feasible and certainly unpalatable, but you remember that the high protein diets we were taught at one time to use were to contain 150 or 175 gm. of protein per 24 hours. That is a lot of protein. The high protein diet we used was somewhere between 100 and 150 gm., depending upon the size and the appetite of the patient. They are certainly harmless in normal livers, they are indicated in patients with hepatitis and cirrhosis and I am very doubtful that the protein itself is the responsible factor in patients who do get confusion and cerebral symptoms in liver failure.

I think that most of those who have espoused the ammonia theory of hepatic coma are abandoning it, that ammonia is probably not the toxic substance. There may be some toxin absorbed from the gastrointestinal tract which results from puterefaction. It depends perhaps on the bacterial flora and it may be in some way related to protein but it is not at all certain, because patients will go into hepatic coma when they are on nothing but intravenous glucose and get no proteins by mouth at all. Some of these patients, as I have reported previously, can be rescued from coma with a large amount of steroids, maintaining a high protein intake. So I do not believe that the high protein diet is injurious in patients with liver disease.

Dr. Wirts:—There were three other questions largely along the same lines which I will have to pass over. Another question is: "What test do you use to determine hypoalbuminemia? Chemical test, the A/G ratio or electrophoretic pattern?"

Dr. Spellberg:—We use a chemical test but it is not the Howe procedure, it is the test that was perfected at our hospital by Wolfson and Cohn (*Amer. J. Clin. Path.* 18:723, 1948) It's a salting-out procedure but it is not the Howe procedure and it gives a value of serum albumin which is equivalent to the electrophoretic procedure.

May I say a word about Dr. Sterling's remark about the bilirubin in the patient that I indicated who had an intrahepatic cholestasis. I was saying that the drop in the bilirubin was a sign of a decrease in the intrahepatic cholestasis, which I think everyone will agree with. In severe hepatitis you may have a patient die without icterus, occasionally. If, however, icterus is present, it almost invariably increases as the patient gets worse and the liver will conjugate bilirubin, producing the bilirubin monoglucuronate. It probably won't produce the diglucuronate, but certainly the bilirubin itself is produced elsewhere and the monoglucuronate is also produced outside of the liver itself.

Dr. Wirts:—Thank you very much, Dr. Spellberg. I have one final question that I would like to present to Dr. Fuchs and the question is: "Please indicate your method of obtaining a high protein diet 200 to 500 mg. of sodium and the diet that a cirrhotic will tolerate." I think the gist of the question is, if it is theoretically correct to give the high protein, high carbohydrate diet and a low sodium diet, how do you get the patient to take it?

Dr. Morton Fuchs (Philadelphia, Pa.):—That is a very good question. It is feasible to calculate a low sodium diet that has high protein content. Admittedly this diet is not a highly palatable diet. I think this is more of a problem for a good dietician rather than myself in all honesty, but I think with condiments and other flavoring substances of various types that the diet can be made palatable enough, if the patient and the physician are persistent enough, so that this can be ingested with beneficial results.

SOME PRINCIPLES OF DIETOTHERAPY*

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Philadelphia, Pa.

Recognition of the dietary needs and their fulfillment are fundamental to dietotherapy. Dietary needs vary in the normal and in the same individual under varying circumstances, normal or abnormal. Disease states in general militate against an adequate dietary intake and the wide range of adaptability which patients exhibit to low vitamin intakes makes it impossible to render conclusions on specific values below which a complicating avitaminosis may be predicted with certainty.

Unless appropriate precautionary measures are applied, malnutrition may develop unnoticed and especially in patients with prolonged illnesses. This possibility was emphasized in the survey of the nutritional intake of all patients, medical, surgical and obstetrical, at the Pennsylvania Hospital. On the medical wards, 37 per cent consumed grossly inadequate diets; 13 per cent consumed less than 1,000 calories daily.

A patient with luetic aortitis, not acutely ill, had an average intake of 17 gm. of protein per day. One with bronchiectasis ingested 29 gm. of protein per day, a trifle more than was lost in his sputum. The latter patient had lost 83 pounds. With correction of this anorexia, a prompt gain in weight and great clinical improvement ensued when appropriate measures were put into effect.

The patients receiving diets low in salt were prone to have subnormal total dietary intake. These unfavorable trends were reversed when the survey focused the physician's attention on the dietary hazards that prevailed.

On the obstetrical and gynecologic service, one woman, 10 days postpartum, consumed 24 gm. of protein per day, and another 8 days postpartum, 42 gm. of protein—the fundamental requisites for the production of milk were not being met. A patient with a uterine fibroid, a candidate for surgery, was consuming 23 gm. of protein and 893 calories per day—not an acceptable preoperative diet.

I was asked to see a malnourished psychiatric patient who had been in a Veterans Administration psychiatric hospital for 25 years. He had decubitus ulcers over his sacral and both trochanteric areas. No other abnormalities beyond his malnutrition, psychiatric disturbances and decubitus complications were observed. Having no desire for food, he illustrates well what I like to call *the anorexia of undernutrition.*

This type of anorexia occurs in the chronically ill patient whose dietary intakes are inadequate for considerable periods and characteristically the an-

*Presented before the Course in Postgraduate Gastroenterology of the American College of Gastroenterology, Philadelphia, Pa., 27, 28, 29 October 1960.

orexia is corrected within two to four days if an adequate diet is actually incorporated into the body economy.

In the case under discussion, this effect was promptly achieved when the diet prescription allowed over 3,000 calories and more than 125 gm. of protein and was presented in three small meals at the orthodox mealtime with formula feedings between meals and at bedtime.

Between two and three months after the strict consideration to his dietary needs a satisfactory recovery was accomplished.

I had the opportunity of visiting two neurologic centers regularly during the latter part of World War II. At one, though the surgery was superior, little consideration was given to the caloric or protein needs of the paraplegic patient with decubitus ulcers. The results were deplorable. At the other hospital, which was Halloran General Hospital, the nutrition team, in addition to good surgery, succeeded in having these patients consume between 3,000 and 5,000 calories per day and from 150 to 275 gm. of protein daily. The results were brilliantly successful.

The malnourished visceroptotic patient is another problem which has interested me for many years. These sad patients complain of exhaustion, loss of appetite, inability to gain weight, nausea on arising, after eating and a feeling of fullness after consuming small fractions of a meal. They are frequently referred with the diagnosis of a polyglandular disease, because their basal metabolism is below normal and the steroid excretion is low. The neurosis invariably present has deepened, as the years passed without improvement in general health and nutrition.

A patient illustrating this phenomenon was 52 years of age, 5 feet 7 inches in height and weighed 113 pounds. Her complaints were: profound weakness and threatened "blackouts" before breakfast, nausea after eating and intractable constipation. These symptoms were precipitated following the loss of weight from 140 to 113 pounds due to a voluntary restriction in diet. This patient exhibited the usual anxiety state, with the firm conviction that she would always be an invalid and subject to polyglandular disease, that she would never be able to gain any weight because many attempts to do so had failed.

She exhibited the physical evidences of undernutrition and visceroptosis. She was admitted to the hospital for treatment. The diet was gradually increased until it exceeded 3,000 calories with 125 to 140 gm. of protein provided in 3 meals with between meal formula feeding. Vitamin supplements were used in therapeutic amounts.

The foot of her bed was raised six inches. A gain in weight promptly ensued, her symptoms gradually subsided and within two months she was, as she stated, "a new woman". When last seen, she was going at "a terrific pace",

had recently put on a big party for her two children home from college, had a happy sparkle in her eye, an observation made by her husband, and she weighed 140 pounds, a gain of 27 pounds

The chronic ill health of these patients is due to their malnutrition and when this is overcome evidences of endocrine disturbances subside, their neurosis is neutralized, a normal state of health is established and is readily maintained if a subsequent loss of weight is prevented. This is not an exceptional result; it is the rule.

Another consideration is *obesity*. Obesity is a prevalent form of malnutrition and influences unfavorably other disease processes and mortality rates.

An unorthodox mode of treatment has brought success when other measures have failed in the management of severe intractable obesity.

The first patient was a physician. When first seen for a mild diabetes and hypertension and overweight in 1948, he was 42 years of age, was 6 foot 2 inches in height and he weighed 326 pounds; in 1954 he weighed 340 pounds. He had not weighed less than 300 pounds since he was in his teens. A *complete fast* was prescribed and followed for 8 days. Fluids without caloric value were allowed and vitamins were given in therapeutic amounts.

The patient expressed surprise that after the first day he had no hunger. In this and other similar cases the disappearance of hunger coincided with the appearance of a mild degree of ketonemia—the plasma is tested as one would test the urine for acetone. No detectable change in the serum electrolyte pattern occurred. The average loss in weight was 2 pounds per day. Clinical improvement ensued, the pound barrier—300 pounds—was eventually broken as a continued reduction ensued after discharge. His weight, four and a half months later, was 256, a loss of 84 pounds.

The same plan of therapy was adopted for a 16-year old girl who weighed 209 pounds. Her loss in weight was approximately 2 pounds per day. In this case, also, the anorexia appeared when a 2-plus reaction for ketonemia developed.

These cases are touched upon because of the refractoriness of the obesity and the good response obtained from short periods of complete caloric starvation. There appears to be a definite association between the appearance of ketonemia and the anorexia which is so acceptable in these cases.

Low calorie diets containing sufficient carbohydrates to prevent the anorexic degree of ketonemia appear to be the reason why these patients cannot tolerate low calorie diets but do tolerate complete fasts very well.

In conclusion, anorexia is the common outcome of undernutrition and is readily corrected and an insatiable appetite often develops if success rewards the efforts to obtain an adequate nutritional intake for two to four days. It is noteworthy: that the physician's responsibility, regarding the patient's nutrition,

does not cease when the appropriate diet is prescribed; that a diet as high and higher than 125 gm. of protein and 3,000 calories with vitamin supplements can be provided in a liter of formula to supplement what solid foods the patient may consume at the orthodox mealtimes; that decubitus ulcers never occur in an adequately nourished patient, except in such patients as the paraplegic in whom sensory disturbances encourage pressure necrosis; that short term, complete fast periods are not objectionable and do provide an inexpensive and effective therapy for those subjects with intractable obesity; and finally, that a high degree of individual consideration of the dietary needs of the acutely, or more especially, the chronically ill is essential if full advantage of nutritional therapy is to be achieved.

THE GASTROINTESTINAL METABOLISM OF VITAMIN B_{12} AND FOLIC ACID*

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I would like to correct one item in the program which says that I am the Chief of Hematology at St. Luke's, out of deference to my senior, Dr. Luis A. Amill, under whom it has been my pleasure to serve for the last 14 years.

It is singularly important to discuss Vitamin B_{12} and folic acid at a gastroenterology congress. Both substances enter the body through the gastrointestinal tract and deficiency of these substances produces gastrointestinal symptoms. Primary disorders of the gastrointestinal tract may cause malabsorption of these two vitamins and the resulting deficiency may in turn obscure the site of the original pathology. Although one could talk about these substances for a long time, I am going to confine my remarks today to the gastrointestinal aspects of Vitamin B_{12} and folic acid.

Both of these substances are enzymes that are essential for the synthesis of nucleic acids. Mitosis depends upon the synthesis of deoxyribose nucleic acid, or DNA, which is the nucleoprotein of the chromatin. A defect in production of chromatin will naturally make a lesion most conspicuous in those tissues with the highest cellular turnover rate; that is, the bone marrow and the gastrointestinal mucous membrane. It has been estimated that the entire lining of the gastrointestinal tract is replaced approximately every four days. Anything interfering with the replacement of these cells could be expected to lead to a variety of gastrointestinal complaints and lesions.

Vitamin B_{12} is unique in having a highly specialized absorption mechanism. Many years ago Castle demonstrated that pernicious anemia patients lacked a heat labile enzyme in their gastric juice which he designated "intrinsic factor" which combined with a substance present in food, called "extrinsic factor", to promote the absorption of the latter. We now know that extrinsic factor is Vitamin B_{12}. Intrinsic factor has not yet been isolated. It is known, however, that it is either a mucoprotein or a substance found in close association with mucoprotein. It has the property of binding Vitamin B_{12} and making it unavailable for bacterial growth *in vitro*.

There are many substances which have this property, but only intrinsic factor can promote the absorption of Vitamin B_{12} across the gastrointestinal barrier. In order for this to occur, the two substances must be given within two or three hours of each other. The nature of the reaction is unknown.

*Presented before the Course in Postgraduate Gastroenterology of the American College of Gastroenterology, Philadelphia, Pa., 27, 28, 29 October 1960.

It has recently been observed that substances present in gastric juice can also promote the uptake of Vitamin B_{12} by liver slices *in vitro*. There is more than one fraction of gastric juice that has this property, but only intrinsic factor can promote the absorption of Vitamin B_{12} from the gut. The presence of calcium ions is essential for both liver slice uptake and intestinal absorption.

The nature of the reaction must be highly specific. Vitamin B_{12} is a coordination complex built around cobalt, and contains a cyanide radical and a dimethylbenzimidazole moiety. Analogues of the vitamin can be made by replacing the cyanide with various inorganic radicals, such as chloride, nitro, thiocyanate, sulfate, etc., and the benzimidazole moiety may also be altered by chlorination, hydroxylation, demethylation, or other procedures.

This slide shows some studies we did which demonstrate the highly specific nature of the chemical reaction involved in the absorption of Vitamin B_{12}. Patients with pernicious anemia in remission were first tested with cyanocobalamine, which is the parent substance, Vitamin B_{12}—and you can see in the first column on the left that none of them absorbed Vitamin B_{12} in any significant amount until intrinsic factor was added. We see that patient JB did have a minimum level for normal absorption without intrinsic factor but that with intrinsic factor it was markedly enhanced. All of the other patients were way below the minimal level.

The next three columns show the failure of absorption of chlorocobalamine, nitrocobalamine and thiocyanatocobalamine, even with intrinsic factor, and in the last three columns we see also that changing the benzimidazole moiety by putting hydroxyl in the 5 position, or by removing the 2 methyl groups, or by substituting chloride for the methyl groups resulted in complete failure of the vitamin to be absorbed. Incidentally these changes were not attended by any loss of biological activity on the part of the vitamin.

We also know that if enough Vitamin B_{12} is given, amounts adequate for nutritional purposes will be absorbed without any intrinsic factor.

When labeled Vitamin B_{12} is ingested in small physiologic doses, it does not appear in the blood stream until 8 to 12 hours later. (Slide) This slide from a paper by Doscherholmen and Hagen, shows that in pernicious anemia patients where large doses of Vitamin B_{12} of 50 mcg. or 100 mcg. were administered with intrinsic factor, maximum blood levels were not achieved until 12 hours after ingestion. When the same dose was given without intrinsic factor, the vitamin began to appear in the blood stream within 2 hours reaching its maximum level at about 6 hours. The level reached in the blood was proportionate to the size of the dose.

(Slide) This diagram shows the gut lumen, in between the mucosal cells, and on the outside, the blood stream. Vitamin B_{12} and intrinsic factor combine in the gastrointestinal tract to form a complex which in turn unites with calcium

ions at the gut wall. This complex in some way facilitates the transfer of Vitamin B_{12} into the cell, where it combines with a receptor protein to form a B_{12} receptor protein complex which remains in the cell for several hours. We may postulate the existence of transferase enzymes in the cells and in the blood stream although as yet they have not been isolated. Their function is to take the B_{12} off of protein complexes and get it across cell membranes and into a new complex where it can be used. In this fashion B_{12} is then taken off the receptor protein in the cell and released into the blood stream where it combines with a globulin which is the B_{12} binding protein of the blood.

Most of the Vitamin B_{12} found in the blood stream is in this bound form, and in this form is transported to the tissues where it is used or to the liver for storage for future use. A certain amount of it is excreted in the bile.

When Vitamin B_{12} in excess of the available binding amounts to intrinsic factor or receptor protein is given, it diffuses directly across the cell membrane by simple mass laws. The free B_{12} does not tarry in the cell but goes on into the blood.

On the basis of responses in pernicious anemia patients in relapse to large doses of Vitamin B_{12} by mouth, it has been estimated that of 1,000 mcg. ingested at one time, approximately 15 mcg. will cross the cell wall into the blood stream where it is bound in the usual fashion and transported for utilization. Only unbound B_{12} appears to pass the renal barrier, so that if one gives 1,000 mcg. by mouth, none will appear in the urine. Injected B_{12}, in excess of 50 mcg. will begin to appear in the urine very rapidly and of a 1,000 mcg. injected dose 95 per cent or more will be excreted in the subsequent 48 hours. This fact is the basis of the radioactive Vitamin B_{12} absorption test of Schilling.

(Slide) In this test, a small dose (usually 0.5 mcg.) of B_{12} labeled with radioactive cobalt is administered orally. Normal subjects will not show any radioactivity in the urine unless the B_{12} binding protein of the blood is simultaneously saturated with an injection of 1,000 mcg. of cold Vitamin B_{12}. Most of this is excreted, as I have just described, and carries with it a part of the labeled material in proportion to the amount absorbed.

Normal subjects under these conditions will excrete from 8 to 30 per cent of a 0.5 mcg. oral dose of labeled B_{12}. Patients with pernicious anemia, in the absence of intrinsic factor, will excrete less than 8 per cent (usually much less) unless the radioactive B_{12} is given together with normal gastric juice or intrinsic factor concentrate, in which case they excrete within the normal range.

Patients with malabsorption syndromes, of which tropical sprue is the prototype, fail to show, for the most part, any enhancement of excretion of labeled material; in other words, they fail to absorb it, even in the presence of intrinsic factor. Some sprue patients have normal Vitamin B_{12} absorption and excretion.

One might surmise from what I have just said that patients with pernicious anemia could be treated with oral Vitamin B_{12} by mouth without intrinsic factor, and that is true, if one gives enough. It has been found that daily oral doses of 100 to 250 mcg. or weekly doses of 1 mg., without intrinsic factor, will maintain pernicious anemia patients in satisfactory hematologic and neurologic remission.

The reason why sprue patients do not absorb the vitamin is probably the lesion of the absorptive surface itself.

In contrast to Vitamin B_{12}, folic acid passes easily across the gut without any such complicated arrangements. It exists in foods in conjugated forms which are not easily split by patients with achlorhydria, but this has no bearing on the pathogenesis of pernicious anemia in which disease folic acid levels are usually normal. Sheehy's studies in Puerto Rico, however, indicate that patients with tropical sprue in relapse who are maintained in the hospital on standardized diets which contain an average of 35 mcg. of free and 1,328 mcg. of conjugated folic acid remained in relapse but showed prompt and excellent response to as little as 25 mcg. of crystalline folic acid given by mouth daily. In other words, if these observations are correct there must be something different about crystalline folic acid as contrasted to food folic acid, in regard to its absorbability by these sprue patients.

The pathogenesis of the folic acid deficiency leading to tropical sprue is obscure. Gluten has been largely absolved from playing any role whatever in the pathogenesis of this syndrome. It has been noticed that there is a geographical association of tropical sprue with populations where animal fat is the principal fat used in cooking, and this has led some to theorize, notably Frazer, on the possibility of rancid fat interfering with the absorption of folic acid. This is an attractive theory which, however, still awaits confirmation.

By this time it is common knowledge, that the permissible levels of folic acid in multi-vitamin capsules has recently been reduced to less than 0.4 mg. per capsule. There are two reasons for this. It is now known that the therapeutic dose of folic acid is considerably less than was previously supposed; therefore, larger doses are unnecessary and merely add to the expense of such products. Of greater importance is the fact that in that small segment of the population with pernicious anemia folic acid may activate or precipitate the neurologic manifestations of that disease.

Without going into the metabolic interrelationships of B_{12} and folic acid, I will say that both are involved in synthesis of DNA for cell formation but only B_{12} plays a role in neuronal metabolism. Since both are involved in the former reaction, the anemia may respond to B_{12}, which is the primary deficiency, or to folic acid by a mass effect. The response to folic acid is limited by the available supplies of Vitamin B_{12}.

In the pernicious anemia patient, who cannot absorb B_{12}, treatment with folic acid speeds up reactions consuming the already depleted supplies of B_{12} leading to their further depletion. When B_{12} levels drop below the value essential for neuronal preservation, combined system disease may develop, often with fulminating rapidity.

It is now generally acknowledged that folic acid is contraindicated in pernicious anemia. Occasional patients turn up who do not know they have pernicious anemia until they develop combined system disease while taking multi-vitamin preparations containing folic acid. It is hoped that reducing the permissible folic acid content of such preparations to less than 0.4 mg. will prevent such occurrences in the future.

Discussion

Dr. Garfield G. Duncan (Philadelphia, Pa.):—"Comment on using alternating low calorie and liberal calorie diets in a weight reduction program."

For some patients this alternating regimen is a very satisfactory plan, 1,200 and 1,600 calorie diets are given on alternating days. On the days that patients consume low caloric diets they look forward to the big one on the following days and the average of the two is a reducing program.

"How do you stimulate the appetite of these very thin, nervous patients who state they cannot eat? Do you believe in the use of Dysorbin or similar preparations?"

I think in malnourished patients the most effective plan is to get food into them for two or three days. Rarely does this fail to restore their appetite. The ordinary meals are usually not successful. In fact, I would say that that which is served at the usual meal time should be looked upon as inconsequential and that the chief caloric intake would be in formula feedings. As was indicated in a formula that was used at Halloran General Hospital during World War II a very liberal diet—2,500 to 4,000 calories—can be provided in one to one and a half liters of fluid. It is a very simple matter to get the patient to drink this amount. It should not be given too abruptly for fear of provoking diarrhea, but I know of nothing that is more effective in restoring appetite to these malnourished patients than the getting of food into them by hook or crook for a few days.

"How much does the patient referred to"—that was the physician patient—"weigh today?"

The last weight that I gave, which was 256 pounds, is his most recent weight and that is four and a half months after eight days of starvation. I might say that he is continuing to decrease in weight, which he was unsuccessful in doing before.

"What did you do to educate the patient in following a diet on solid food for the rest of his life?"

I think that with the weight corrected, one needs to watch the total calories and have the dietitian provide the diet in bulky form that may be more satisfying than a concentrated diet. These patients should be followed with the idea that there are going to be alterations in this program from time to time.

Question:—In your experience are the changes in the pattern of the mucosal membrane reversible after the blood improves B_{12} or folic acid with sprue?

Dr. Edward H. Reisner, Jr. (New York, N. Y.):—I think that it is partly a matter of duration of the deficiency. There is no question that long-standing deficiency will produce irreversible lesions in the gastrointestinal tract. Of particular interest in that connection is the fact that in the rare cases of pernicious anemia that are encountered in children where the disease has not existed for a long time we found, in the four patients we reported that during relapse they would have glossitis and achlorhydria but following remission the gastric HCl returned, and the glossitis disappeared. Aspiration biopsies of the mucosa of the stomach in these patients during remission showed perfectly normal looking mucosa. I think we might postulate that as a result of the Vitamin B_{12} deficiency an inflammatory reaction was produced which, if it was not of too long duration, was certainly reversible.

Dr. Wohl:—Dr. Reisner, have you seen an instance of pernicious anemia developing neurologic symptoms following folic acid, personally?

Dr. Reisner:—Oh, yes.

Question:—Do you think it is the folic acid, or do you think it is because the patient absorbs the B_{12}, the folic acid masks the anemia and then it is the B_{12} deficiency that produces the degenerative change rather than the folic acid.

Dr. Reisner:—It is the B_{12} deficiency, not the folic acid. The first one we saw like that was a patient that we were treating with folic acid for pernicious anemia and we were very pleased with the nice hematologic response. Then, one day she came staggering in to the clinic and the change was so abrupt that I did not suspect what was going wrong; I thought she had had a stroke. Careful examination showed that she had typical findings of combined system disease and we realized that this was a case similar to one that had just been reported by Berk. We took her off folic acid and gave her liver extract—we didn't have B_{12} yet—and she did very nicely.

Question:—Concerning folic acid in multi-vitamin capsules, what is the dose that would be a safe dose to include?

Dr. Reisner:—The current decision of the Council of placing the level at 0.4 mg. to my way of thinking may be a little too high, because a patient might

take several capsules a day containing 0.4 mg. and get a larger amount. I think, however, that in general that level is agreed to be low enough so that it is not likely to get patients with pernicious anemia into trouble.

Dr. Duncan:—Another question is: "I could not hear your recommendation on the starvation routine in difficult obese cases to produce ketonuria."

The obese patients from whom all exogenous food is withdrawn are to all intents and purposes on an extraordinarily high fat diet, the fat being drawn from endogenous sources. In the absence of ingested carbohydrate, ketones are produced in increasing quantities and appear in the urine in increasing amounts. Shortly, in a day or two, the amount of ketones produced exceeds the patients' ability to excrete the excess amounts and ketonemia becomes detectable. It is when the ketones are detectable in the plasma that the anorexia is noted in the patients on a starvation regimen. The test for ketones in the plasma is the same as the test for acetone in the urine, but one must not use the ketonuria as the guide. *It is the ketonemia that produces the anorexia* which is an index of production of prodigious amounts of ketones.

On the regimen of starvation, water, weak tea, artificial sweetening agents and "no-cal" drinks are allowed as desired. Multiple vitamins are given in therapeutic amounts.

AN EXPERIMENTAL STUDY OF N-(3-PYRIDYLMETHYL) DIBENZYLAMINE DIHYDROCHLORIDE (Ro 2-7983) ON THE GASTROINTESTINAL TRACT

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It has been claimed that a drug that is capable of inhibiting the secretion of acid by the stomach would be efficacious in the treatment of peptic ulcer[1], Banthine and Pro-Banthine have been the subject of intensive study by several groups of investigators[2-4]. Banthine is a quaternary ammonium salt; Pro-Banthine is the isopropyl analogue of Banthine. In small amounts, Banthine inhibits structures innervated by postganglionic cholinergic nerves and blocks the action on these structures of injected acetylcholine. Somewhat larger doses block transmission through autonomic ganglia and still greater concentrations have a curariform effect. Dragstedt[5] has noted inhibition of human gastric secretion.

Khellin has been reported by Desmarez[6] to have the property of suppressing gastric secretion.

This report is concerned with the experimental demonstration that Ro 2-7983 [N-(3-pyridylmethyl)dibenzylamine dihydrochloride] and Ro 2-7794 [N-(4-pyridylmethyl)dibenzylamine dihydrochloride] inhibited gastric ulcer formation in the Shay rat, histamine-induced ulcer in the rat and provided considerable protection against jejunal ulcer in the Mann-Williamson dog, constituting experimental indications for potential usefulness as an antiulcer agent. The compounds were supplied by Gardner, Wenis and Lee[7] who described the method of preparation of Ro 2-7983 [N-(3-pyridylmethyl)dibenzylamine dihydrochloride] and Ro 2-7794 [N-(4-pyridylmethyl)dibenzylamine dihydrochloride]. Experimental studies on Banthine, Pro-Banthine, atropine and Khellin are also included in this report.

Methods

Shay test:—Male and female rats weighing between 120-160 gm. were prepared by the method of Shay and coworkers[8]. The animals were starved for 48 hours and water permitted *ad libitum*. At the end of the 48 hours' starvation, the rats were subjected to light ether anesthesia, the pylorus was ligated through a small midline incision. Eighteen hours later the surviving animals were sacri-

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ficed and all the animals were autopsied. The stomach was removed and the gastric contents drawn into a graduated cylinder, measured and analyzed for pH, free, combined and total acid. The stomach was split along its entire greater curvature, laid open and examined for ulceration. The degree of ulceration was evaluated according to Figure 1a.

Gastric analysis:—Gastric pH determinations were made by a Beckman electrometric apparatus using the entire filtered gastric contents. The gastric

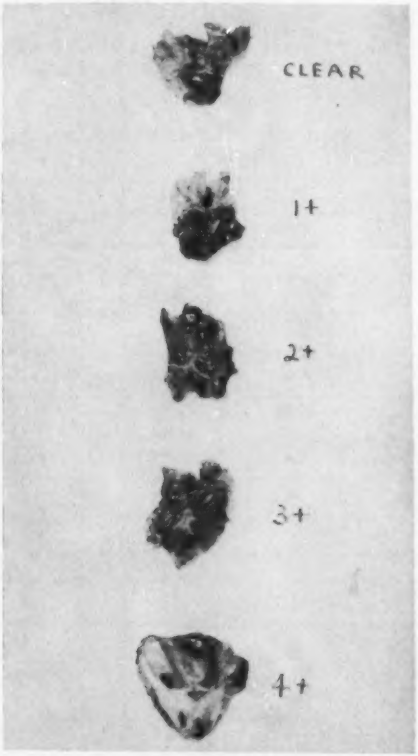

Fig. 1—Evaluation of results. Degree of ulceration.

juice was measured for volume and titrated for free acid to the salmon pink end-point of Topfers' reagent, using N/10 NaOH. The results are expressed in clinical units—the ml. of N/10 NaOH required to neutralize 100 ml. of gastric juice. Milligrams of HCl are calculated as follows:

Clinical units x volume in ml. x 0.365

TABLE I

THE ANTIULCER EFFECT OF VARIOUS AGENTS IN SHAY RATS 18 HOURS AFTER PYLORIC LIGATION

Drug	Dose mg./kg. S.C.	No. of rats	Degree of ulceration					Average degree of ulceration	Average volume secretion	Average pH	Total mg. HCl
			0	1+	2+	3+	4+				
Controls	—	20	0	0	0	4	16	3.8	2.4	1.9	3.2
Atropine	5	20	4	4	2	6	4	2.1	0.8	2.1	4.3
Atropine	10	20	7	7	3	2	1	1.2	0.6	1.7	4.1
Banthine	2.5	20	9	4	2	2	2	1.1	2.8	2.7	5.0
Banthine	5	20	4	3	9	3	1	1.7	1.9	3.1	5.2
Pro-Banthine	2.5	10	3	4	1	1	1	1.2	2.7	3.3	5.2
Pro-Banthine	5	10	4	4	0	1	1	1.1	2.4	2.9	4.9
Khellin	5	10	4	3	1	1	11	1.2	2.0	3.0	5.3
Khellin	10	20	9	3	5	2	1	0.9	2.3	2.4	5.0
Khellin	20	20	13	3	0	4	0	0.6	2.0	2.8	5.1
Ro 2-7794†	5	10	7	1	1	0	1	0.7	1.9	1.7	4.4
Ro 2-7794†	10	10	7	2	0	0	1	0.6	2.7	2.6	5.0
Ro 2-7983*	5	10	6	2	0	1	1	0.9	5.2	2.4	5.3
Ro 2-7983*	10	10	7	2	1	0	0	0.5	6.8	2.2	5.5

†N-(4-pyridylmethyl)dibenzylamine dihydrochloride as 10% solution at pH 2.4 using HCl

*N-(3-pyridylmethyl)dibenzylamine dihydrochloride as 10% solution at pH 2.4 using HCl

Histamine-induced ulcer in rats:—Rats weighing between 120 and 160 gm. received daily by intramuscular injection 90 mg. histamine phosphate in a mixture of beeswax and mineral oil, prepared according to Varco[9] and Code[10]. Following periods of 10 days to 3 weeks animals became anorexic, lost weight and died of a perforating gastric ulcer or a perforating ulcer in the first portion of the duodenum. Thirty animals were used in each experiment, 20 received the test drug and ten animals served as controls. The treatment of surviving animals was carried on for 30 days after which time they were sacrificed and autopsied.

Mann-Williamson dog:—This preparation is often referred to as a duodenal drainage. The gastric contents are diverted into the jejunum by isolating the

TABLE II

THE EFFECT OF VARIOUS DRUGS ON SURVIVAL TIME ON THE HISTAMINE-INDUCED ULCER IN THE RAT

Drug	Dose mg./kg.	No. of rats	Survival time in days	No. died of perforated ulcer	Total ulcer incidence %
Control		10	12,12,13,13,13,14,15,17,19,20	10	100
Atropine	5	10	14,14,15,17,18,18,18,20,23	9	90
Atropine	10	10	15,16,19,19,19,20,24,29	8	80
Banthine	10	10	20,21,25,29	4	40
Pro-Banthine	10	10	23,24,26,29	4	40
Khellin	10	10	14,15,19,24,24	5	50
Ro 2-7794†	10	10	19,20,22,27	4	40
Ro 2-7983*	10	10	18,21,29	3	30

†N-(4-pyridylmethyl)dibenzylamine dihydrochloride as 10% solution at pH 2.4 using HCl
*N-(3-pyridylmethyl)dibenzylamine dihydrochloride as 10% solution at pH 2.4 using HCl

duodenum, cutting it away from the pylorus and the jejunum. The pancreatic and biliary secretions are discharged into the lower part of the bowel (ileum). Surgical anastomoses are made between the stomach and distal jejunum and the distal duodenum and ileum. The proximal duodenum is closed. In the Mann-Williamson dog, ulcers develop just distal to the gastrojejunal anastomosis. Hemorrhage or jejunal perforation is the common cause of death in this preparation[11].

RESULTS

Table I summarizes the data on the preparations evaluated according to the method of Shay. It is observed that three preparations, Ro 2-7794, Ro 2-7983

and Khellin, decreased the number of ulcers and the number of perforations. No perforations occurred following the administration of 10 mg./kg. Ro 2-7983, Ro 2-7794 and Khellin in contrast to three, three and two perforations, respectively observed with 10 mg/kg. atropine, Banthine and Pro-Banthine. A lower dose of these preparations has a proportionately lesser effect. The volume of gastric juice (stomach contents) found in rats was more with Ro 2-7983 and

TABLE III

SURVIVAL TIME OF MANN-WILLIAMSON DOGS

Drug	Dose mg./kg.	Route	Survival (days)	Remarks
Control	(saline)	Oral	20	Perforated jejunal ulcer
Control	(saline)	I.M.	34	Perforated jejunal ulcer
Control	(saline)	I.V.	36	Perforated jejunal ulcer
Atropine	5	Oral	49	Perforated ulcer, hemorrhage
Banthine	5	Oral	50	Perforated ulcer, hemorrhage
Banthine	10	Oral	48	Perforated ulcer, hemorrhage
Pro-Banthine	10	Oral	63	Perforated ulcer, hemorrhage
Khellin	10	Oral	60	Emaciation, bronchopneumonia, mange, no ulcer
Ro 2-7794†	5	Oral	69	Hemorrhage—small jejunal ulcer
Ro 2-7794†	10	Oral	64	Perforated jejunal ulcer
Ro 2-7983*	5	Oral	86	Hemorrhage—small jejunal ulcer
Ro 2-7983*	10	Oral	89	Hemorrhage—small jejunal ulcer, bronchopneumonia

All animals received daily by intramuscular injection 60 mg. total dose histamine phosphate in beeswax and mineral oil.
†N-(4-pyridylmethyl)dibenzylamine dihydrochloride as 10% solution at pH 2.4 using HCl
*N-(3-pyridylmethyl)dibenzylamine dihydrochloride as 10% solution at pH 2.4 using HCl

Ro 2-7794 than with atropine, Banthine and Pro-Banthine. There were no significant effects on free HCl with Ro 2-7983 and Ro 2-7794.

Figure 1b shows the appearance of the rats' stomachs 18 hours after pyloric ligation. Groups of animals were given 10 mg./kg. of Ro 2-7983, Ro 2-7794, Khellin, atropine, Banthine or 5 mg./kg. s.c. Pro-Banthine. No hyperemia or gastric ulcer was evident from gross appearance of the specimens in animals pretreated with Ro 2-7983. Rats treated with atropine, Banthine, Pro-Banthine

TABLE IV

THE EFFECT OF RO 2-7983 ON THE GASTRIC SECRETION IN THE HAIDENHAIN POUCH OF DOGS STIMULATED WITH 1 MG. HISTAMINE INTRAMUSCULARLY

Dog	Dose mg./kg.	Control			1 hour			2 hours		
		Vol.	pH	HCl mg./Hr.	Vol.	pH	HCl mg./Hr.	Vol.	pH<	HCl mg./Hr.
"Whitie" Wt. 9.1 kg.	0	8.1	3.4	1.64	13.2	1.9	1.92	11.0	2.6	1.40
	5	11.6	3.0	1.72	18.4	2.2	1.68	16.0	2.4	1.66
	8	15.2	5.1	2.14	17.6	2.0	2.12	15.1	3.7	1.80
	10	14.0	4.8	2.10	16.8	2.1	2.12	18.2	3.4	1.90
	16	12.2	2.8	1.80	19.7	1.1	0.98	16.3	3.1	1.42
"Peanuts" Wt. 6.7 kg.	0	5.2	4.0	1.10	7.6	1.8	0.92	10.2	2.4	1.00
	5	6.6	3.4	1.34	8.2	1.9	0.90	15.2	3.9	1.48
	8	10.2	4.6	1.36	12.4	2.4	0.78	17.8	3.2	0.89
	10	9.4	3.8	1.04	16.6	2.1	1.08	19.8	2.6	1.02
	16	13.0	3.1	1.94	16.9	1.9	0.92	19.2	3.8	1.84

and Ro 2-7794 showed a moderate to marked degree of ulceration. There was a lack of protection against rumenal ulcer. In a number of cases, perforated gastric ulcers were observed.

The effect of the preparations on histamine-induced ulcer in the rat is illustrated in Table II. Animals expired at various intervals during the 30-day period from perforated ulcers. In agreement with the results in the Shay test,

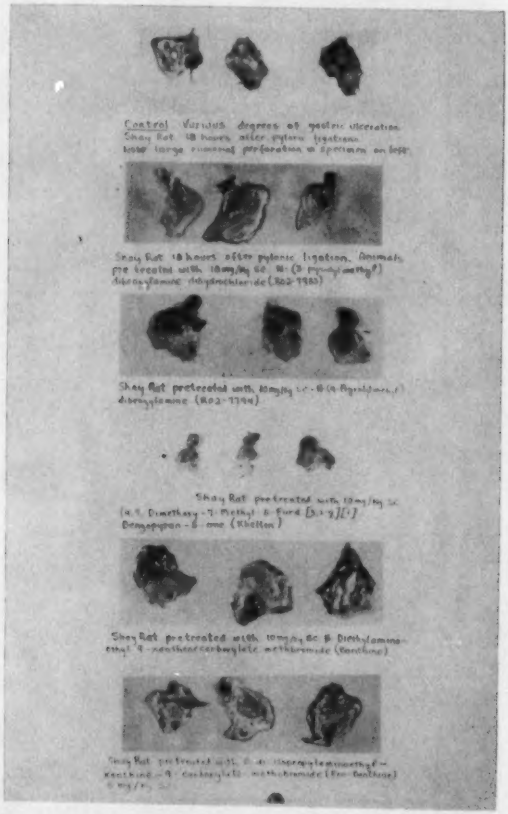

Fig. 1b—Rats' stomach, 18 hours after pyloric ligation. Control and pretreated animals.

Ro 2-7794, Ro 2-7983 and Khellin had a definite prophylactic effect against histamine-induced ulcer formation. Atropine, Banthine and Pro-Banthine had a moderate effect. Although all rats lost weight during the course of the experimental period, the survival time was markedly prolonged with preparations Ro 2-7983, Ro 2-7794 and Khellin.

The effect of the Ro 2-7983, Ro 2-7794 and Khellin on survival time of Mann-Williamson dogs is illustrated in Table III. It was observed that all 3 compounds are effective to some degree in protecting the animals against jejunal ulcer formation. Atropine, Banthine and Pro-Banthine are moderately active.

The effect of Ro 2-7983 on the gastric secretion in Haidenhain pouch dogs:—Haidenhain pouch dogs[12] were fasted for one day before each study. Gastric secretion was stimulated by the intramuscular injection of 1 mg. histamine phosphate; the Ro 2-7983 was injected intravenously. The output of HCl was calculated from the volume.

Two experiments were performed on 2 dogs, at each dose (Table IV). In each instance, there was an increase in volume with little or no corresponding change in free HCl.

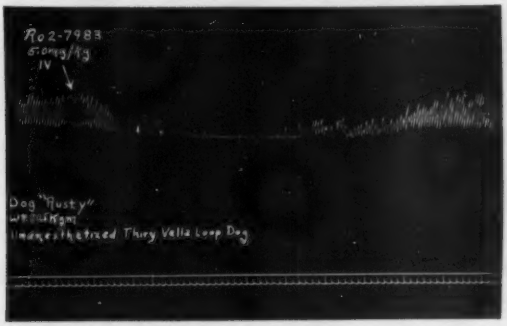

Fig. 2a—Effect of Ro 2-7983, 5mg./kg. i.v., on intestinal activity in a Thiry-Vella loop dog.

Inhibition of gastric acid was not evident in any of the experiments with Ro 2-7983; a consistent increase (Table IV) occurred in gastric volume in all experiments during the first 30-minute collection period. The increase in gastric volume persisted for 1½ hours. The fact that the pH was slightly higher during the second hour may be accounted for by the presence of mucus in the Haidenhain pouch juice.

Spasmolysis in Thiry-Vella dogs:—Seven Thiry-Vella loop trained unanesthetized dogs were utilized in this study. Intestinal activity was measured by a balloon in the isolated jejunal loop. Tone and motility were estimated by taking into account frequency and amplitude of contractions. Motor activity was assessed by the bolus technic by measuring the transit time of a cotton bolus to traverse an innervated Thiry-Vella loop.

Figure 2a shows a slight depression in tone and no effect in the motility of the jejunum with Ro 2-7983 at 4 mg./kg. given intravenously. In oral doses of up to 16 mg./kg. there was slight depression in tone with no effect on the

peristaltic activity. Ro 2-7794 had no effect on tone or motility of the jejunum. In Figure 2b it can be seen that Ro 2-7983 slightly increased the transit time of a cotton bolus through an innervated jejunal loop at the 5 mg./kg. dose level.

Gastric mucin production:—Pyloric pouches were prepared by transecting the pylorus at the duodenum and at its junction with the body of the stomach. The duodenum and the proximal end of the pylorus were closed utilizing the double layer technic. An end-to-end anastomosis of the stomach and duodenum was made to restore the continuity of the bowel. The distal end of the pylorus was brought out through a stab wound in the right upper abdominal region.

TABLE V

EFFECT OF RO 2-7983, ATROPINE SULFATE AND RESERPINE ON THE VOLUME OF SECRETION FROM POUCHES OF THE PYLORIC PORTION OF THE DOG'S STOMACH

Dog no.	Before drug administration	Drug dose	During drug administration	Difference	Per cent change
17A	0.8	Ro 2-7983 10 mg./kg.	1.0	0.2	+ 25.0
	0.5		0.4	− 0.1	− 20.0
	0.7		0.7	0	0.0
20A	0.8	Atropine sulfate 1 mg./kg.	0.4	− 0.4	− 50.0
	0.6		0.1	− 0.5	− 83.0
	0.4		0.1	− 0.3	− 75.0
22A	1.3	Reserpine 1 mg./kg.	2.9	1.6	+123.0
	0.1		1.9	0.9	+ 90.0
	0.7		1.7	1.0	+142.0

Juice from the pouch was collected at 20-minute intervals in a small beaker, using a small soft rubber catheter and a syringe. The drugs were given by continuous intravenous infusion or by the subcutaneous route.

The data in Table V show that 1 mg./kg. of atropine sulfate markedly suppresses gastric mucin production in a pyloric pouch dog. Within 10 to 35 minutes after administration of atropine sulfate, inhibition of gastric mucin was almost complete. No significant suppression or stimulation was observed with the subcutaneous administration of 10 mg./kg. Ro 2-7983. Reserpine increased the secretion of mucin from the pyloric mucosa in pyloric pouch dogs.

The effect of Ro 2-7983 on the pH of the gastric mucosa in the anesthetized dog:—Through a gastrostomy, direct measurements of the pH of the mucosa at seven definite areas in the stomach were made electrometrically by inserting

the electrodes of the Beckman pH meter through a defect in the anterior antral wall[13].

The figures in Table V indicate that the residual pH level of the gastric mucosa after histamine is considerably lowered.

The pH of the gastric mucosa is not altered by 8 mg./kg. Ro 2-7983 i.v. and the reaction to histamine stimulation is not affected.

Effects of caffeine on gastric acidity in dogs:—The method of Lovi[16] with a modification by Roth[17] was employed; 0.5 gm. of caffeine with sodium benzoate in 200 c.c. of water was given through a stomach tube. Aspiration of the contents was resumed ½ hour later and continued for 2 hours, unless the secretory rate had returned to or below the basal level at the end of 1½ hours.

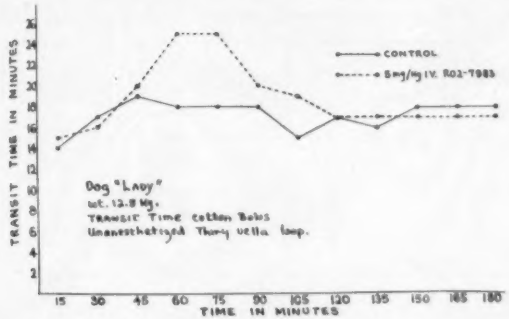

Fig. 2b—The motor activity of the jejunum in the Thiry-Vella loop dog. Assessed by the bolus technic.

Figure 3 demonstrates the secretory response of the stomach to the injected solution of caffeine before and after Ro 2-7983. The average secretory response in 4 dogs was 7.0 mEq. per hour before Ro 2-7983 and 6.5 mEq. per hour after 16 mg./kg. i.v. Ro 2-7983—a decrease of 8 per cent. In all four dogs, a slight decrease in secretory response to caffeine was observed and in no instance was an anacidity noted.

The effect of insulin on gastric acidity:—Insulin hypoglycemia produces an increase in gastric secretion. This action is usually abolished by vagotomy or with atropine.

The basic method which was employed was first described by Simici[18] who reported the effect of intravenously administered insulin on the secretion of the stomach. Five units of insulin was given to a normal mongrel dog and the response to insulin hypoglycemia observed. A control period of basal secretion was observed for ½ hour to 1 hour. The stomach was aspirated continuously and a specimen collected at 15-minute intervals for acid determinations. An injection of 5 units of regular insulin was given intravenously; the stomach

aspirated continuously for 1½ hour to 2 hours following insulin and Ro 2-7983 administration.

Figure 4 shows that there was a maximal decrease in gastric acidity at 30 minutes following 5 units of insulin i.v. in the dog. The increase in free acid is usually noted between 45 minutes and 1 hour, starting at the height of the hypoglycemic action. The graph illustrates that following 8 and 16 mg./kg. Ro 2-7983 the same marked acid response was observed as in the control animals.

Effect of Ro 2-7983 on gastric secretion in the normal anesthetized dog with and without histamine stimulation:—Following a period of ½ hour to 1 hour

TABLE VI

pH of Gastric Mucosa Before and After 8 and 16 mg./kg. i.v. Ro 2-7983
Average Figures from Six Animals

	Control			8 mg./kg. i.v. Ro 2-7983			16 mg./kg. i.v. Ro 2-7983			8 mg./kg. i.v. Ro 2-7983 +1 mg. hist. PO_4 i.m.		
	Residual	15 min. after histamine	30 min. after histamine	Residual	15 min.	30 min.	Residual	15 min.	30 min.	Residual	15 min.	30 min.
Pylorus	4.4	2.2	2.3	4.6	4.5	4.8	4.2	4.0	4.4	4.0	2.0	2.2
Anterior antrum	4.2	2.8	2.6	4.7	4.0	4.2	5.1	4.9	4.1	4.7	3.1	2.8
Posterior antrum	5.4	3.2	2.9	5.2	4.1	4.0	5.0	4.2	4.1	5.0	3.0	3.0
Lesser curvature	4.2	3.1	3.0	4.6	3.8	3.6	4.6	4.4	4.0	4.2	3.8	2.8
Greater curvature	4.4	2.1	1.8	4.8	4.4	4.0	4.0	3.3	3.5	3.8	2.0	1.9
Fundus	3.9	3.0	2.0	4.2	3.9	3.9	3.9	3.0	3.0	4.2	2.4	1.9
Cardia	3.7	2.8	2.1	4.0	3.7	3.4	4.2	3.6	3.4	4.0	2.9	2.3
Composite averages	4.1	2.9	2.3	4.6	4.0	3.9	4.5	3.8	4.0	4.3	2.8	2.5

of basal secretion, an intramuscular injection of 1.0 mg. of histamine phosphate was given to an anesthetized gastric intubated dog. Aspiration of the stomach was continued as during the basal period and the sample measured, a pH reading obtained and titrated for free HCl.

The comparative results in the drug and control series appear in Tables VII and VIII. From these figures, it is apparent that Ro 2-7983 had no significant effect on pH and free HCl following the administration of 8 and 16 mg./kg.

i.v. The increase in volume of secretion with histamine stimulation was not blocked by the intravenous injection of Ro 2-7983.

Banthine and Pro-Banthine have been shown clinically to be of value in the control of symptoms of gastric and duodenal ulcer. Their beneficial effects are thought to result from a depression of gastric secretory and motor activity which has been demonstrated in experimental animals by Code[14] and Walters[15] in man.

The numerous drugs which act primarily on the gastrointestinal tract have been repeatedly studied with a variety of biological and chemical methods of assay.

Although the Shay test has been the subject of criticism by some, it still serves as a significant criterion in the evaluation of antiulcer drugs. The anti-

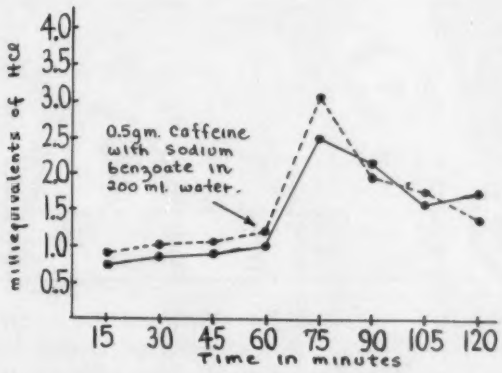

Fig. 3—A composite curve demonstrating the effect of caffeine on gastric acidity before and after 16mg./kg. i.v. Ro 2-7983/1 (Average of 4 tests).

ulcer effect of the various agents injected into the Shay rat has by some experimenters been considered secondary to a nonspecific toxic response and not related to a specific factor present in substances. This investigation has shown that the pylorus ligated rat (Shay rat) can be protected against rumenal ulcer by Ro 2-7983 and Ro 2-7794.

Recognizing the facts so far presented, that Ro 2-7983 and Ro 2-7794 exert definite effects in inhibiting gastric and duodenal ulceration under experimental conditions, it remains to be shown whether the effects are produced through neutralization of gastric juice or actual inhibition of secretion. Evidence bearing on these points were available from several sources. Noting in the gastric analysis the total mg. of acid secretion and the concentration per c.c. such experiments did not present evidence of the efficacy of these compounds in

suppressing or enhancing gastric flow. There has been definite evidence demonstrating that these compounds nullify the powerful effects of the prolonged administration of histamine on gastric acidity.

TABLE VII

AVERAGE BASAL SECRETION BEFORE AND AFTER RO 2-7983 IN THE ANESTHETIZED DOG (AVERAGE FROM SIX DOGS AT EACH DOSE)

Drug	Dose mg./kg. i.v.	Clinical Units Free HCl Time				
		Residual	15	30	45	60
Control	—	18	28	34	38	44
Ro 2-7983	8	26	38	30	24	30
Ro 2-7983	16	22	42	32	36	44
		Volume Secretion in ml.				
Control	—	12.2	8.0	5.8	5.3	6.2
Ro 2-7983	8	18.1	9.4	10.2	10.6	11.1
Ro 2-7983	16	7.0	7.8	9.4	10.2	10.0
		pH				
Control	—	3.9	3.1	2.8	2.9	2.8
Ro 2-7983	8	3.2	2.7	3.1	3.4	3.0
Ro 2-7983	16	3.6	3.1	3.1	2.2	3.1

To test the curative effects of Ro 2-7983 and Ro 2-7794 the histamine, beeswax and mineral oil mixture was administered to two dogs until bloody stools were noted. They were then operated upon, and ulcers in the duodenum

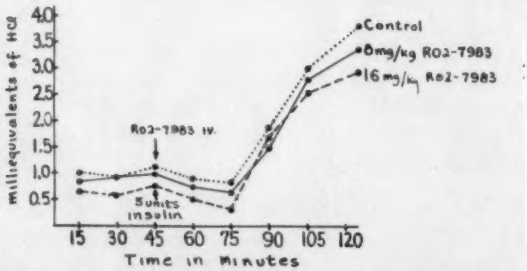

Fig. 4—The effect of insulin on gastric acidity before an after Ro 2-7983/1.

observed. This was then closed; and the animals were started on 5 mg./kg. orally of the preparations two times a day. Unfortunately, the animal receiving

Ro 2-7794 died 72 hours after operation of bilateral bronchopneumonia, but in the animal receiving Ro 2-7983, autopsy 5 weeks later showed the duodenum to be fairly normal despite the fact that the administration of histamine, beeswax and mineral oil in the same dosage had been continued throughout the postoperative period.

Control experiments showed that Ro 2-7983 produced profound effects in the recorded data. Antagonism between injected histamine and Ro 2-7983 was evident whether histamine was given before the injection of Ro 2-7983 or whether the two drugs were previously mixed. When Ro 2-7983 was given after histamine and when the effects of the latter were maximal it was possible to

TABLE VIII

AVERAGE SECRETION BEFORE AND AFTER RO 2-7983 IN THE ANESTHETIZED DOG HISTAMINE STIMULATED SECRETION (1 MG. HISTAMINE PO_4 I.M.)

Drug	Dose mg./kg.	Clinical Units Free HCl Time				
		Residual	15	30	45	60
Control	—	38	72	80	60	44
Ro 2-7983	8	22	66	92	70	40
Ro 2-7983	16	28	52	78	72	48
		Volume Secretion in ml.				
Control	—	6.2	15.4	18.0	9.2	9.0
Ro 2-7983	8	12.9	16.1	20.0	11.8	11.2
Ro 2-7983	16	21.4	17.0	19.6	12.4	10.3
		pH				
Control	—	4.6	2.1	1.9	2.9	2.6
Ro 2-7983	8	3.8	1.9	1.7	2.0	2.1
Ro 2-7983	16	3.1	2.0	2.1	2.8	2.9

demonstrate neutralization of effects already present; e.g. production of ulcer in dog with daily large doses of histamine, visualization of duodenal ulcer, showing disappearance of symptoms and healing of ulcer by moderate doses of Ro 2-7983.

Whether or not the occurrence of healing can be correlated to the quantitative changes in the gastric or duodenal mucosa by different doses of Ro 2-7983 cannot be determined until a wider range of drugs are studied, but it is suggested that the procedures employed in our study might be helpful in determining this potential.

Summary

The antiulcer effects of N-(3-pyridylmethyl)dibenzylamine dihydrochloride (Ro 2-7983) and N-(4-pyridylmethyl)dibenzylamine dihydrochoride (Ro 2-7794), atropine, Banthine, Pro-Banthine and Khellin were striking in Shay rat experiments. These preparations showed a definite prophylactic effect against experimental ulcer in the rat.

The life span of the Mann-Williamson dog was markedly extended with Ro 2-7983.

The pH of the dog gastric mucosa was not altered following the intravenous injection of 8 and 16 mg./kg. Ro 2-7983.

An increase in volume of secretion was observed after Ro 2-7983 in the normal anesthetized dog and in the Haidenhain pouch dog. Ro 2-7983 did not block histamine-induced increase in volume. There was no significant change in pH or free HCl.

The secretory response of the dog stomach to caffeine was not influenced by Ro 2-7983.

Insulin hypoglycemia produced an increase in gastric secretion. Ro 2-7983 did not influence this action at the 8 and 16 mg./kg. intravenous dosage level.

A single intravenous or subcutaneous dose of 5 mg./kg. Ro 2-7983 reduced intestinal tone and moderately decreased the propulsive activity of the jejunum in Thiry-Vella loop dogs.

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CLINICAL TRIAL OF A NEW LONG-ACTING ANTACID-ANTISECRETORY COMPOUND*

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The wide variety of presently available antacids share the common disadvantage of short duration of action, presumably due to rapid gastric emptying, and result in transient neutralization of gastric juices. To be effective a simple antacid must be taken frequently. This is an inconvenient and costly regimen to which few patients remain faithful for any length of time. Various combinations of antacids and anticholinergic drugs have been tried in an effort to prolong antisecretory action. While the new synthetic anticholinergic agents possess some advantages over the older belladonna preparations, there is still some question as to their over all superiority with respect to lessened toxicity. effectiveness and necessity for frequent administration. In fact, among many gastroenterologists one finds a return to or continuance of the use of galenical belladonna preparations as dependable antisecretory and antimotility agents in the management of peptic disorders. With the availability of better pharmaceutical preparations of *Atropa Belladonna* such as Bellafoline ®†, which contains the natural levorotatory alkaloids of belladonna, even more favor is being shown now in the use of belladonna alkaloids over synthetic preparations[1,2].

Recently, an improved combination of an antacid anticholinergic preparation has been made available as BepHan Spacetabs®†. This tablet is composed of 450 mg. of alminum hydroxide and glycine, 60 mg. of magnesium oxide and 0.5 mg. of Bellafoline. The rationale for this particular combination is based on the premise that the immediate release of Bellafoline reduces gastric motility and delays emptying into the small intestines, thus allowing prolonged contact between the antacid and the gastric juice. Glycine was added for its buffering action to prolong the action of aluminum hydroxide, and the magnesium oxide, itself a nonabsorbable neutralizing agent, included to counteract the constipating effects of aluminum hydroxide. The manufacturer's recommended dosage was 1 BepHan Spacetab morning and evening after meals, increased to three tablets daily if necessary.

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†Products of Sandoz Pharmaceuticals, Hanover, N. J.

Weiss et al[3] first reported on the clinical trial of BepHan Spacetabs in 158 patients for the treatment of a wide variety of gastrointestinal disorders. Their paper presents representative case reports where rapid and effective symptomatic improvement was achieved as well as notable decreases in free hydrochloric acid and total acid. A majority of their patients were able to remain symptom-free with side-effects with only 2 BepHan Spacetabs per day. Hock[4] observed the same satisfactory response to BepHan Spacetabs in the treatment of 109 patients seen in office practice while King[5] found this new combination "extremely effective in relieving the diverse symptoms" exhibited by the 78 patients he treated. Similarly, in a partly statistical laboratory and clinical evaluation of BepHan, Guth and Allen[6] obtained good results in a majority of 45 patients when the tablets were given one hour after meals and at bedtimes.

TABLE I

Diagnosis of Peptic Disorders in 59 Patients Given Trial of BepHan

Diagnosis	Number of patients	
	Diagnosis proven	Diagnosis probable
Duodenal ulcer	20	6
Gastric ulcer	13	1
Esophageal ulcer	2	
Hiatus hernia	7	
Gastritis	7	
Esophagitis	3	

The purpose of this paper is to report the results of a clinical study of the trial of BepHan Spacetabs in 50 patients over a 6 months' period in comparison with the routine modified Sippy employed for many years in this hospital and clinic.

Methods and Materials

Patients:—All patients included in this study were selected from the hospital wards. As many of these as possible were continued on therapy and followed subsequently as outpatients. Forty-three men and 16 women whose age averaged 62 years were given trial of BepHan Spacetabs. The diagnoses (Table I) for these patients were based chiefly on the history and physical examination with the ancillary help of radiographic studies, stool examinations for blood, and urine measurements. Other routine laboratory work was performed.

Procedure:—Response to BepHan therapy was to be gauged by: 1. subjective symptomatic improvement of the patient and the patient's acceptance of a

reduced schedule of administration of the medication; 2. measurement of titratable gastric acidity before and after institution of BepHan therapy and, for comparison, before and after use of modified Sippy regimen*; and 3. roentgenologic laboratory studies following a period of treatment with BepHan.

Dosage:—Where the condition of the gastric disorder permitted, BepHan therapy was to be restricted to the recommended dosage of 2 or 3 tablets daily. When required to lessen the distress of the patient, pHan† tablets plus milk and cream were to be employed on an hourly basis or less frequently if possible.

Results

It was possible to start 21 hospitalized patients on BepHan Spacetabs by giving 3 to 4 tablets daily with hourly pHan tablets plus milk and cream. Another group of 38 patients were placed first on the modified Sippy regimen because of the acuteness and severity of their symptoms. After approximately 5 days when the acute symptoms had abated, both groups were transferred to therapy with only 3 to 4 BepHan Spacetabs for the remainder of the treatment period.

The response to early treatment was more successful in the group started initially on the modified Sippy regimen with 92 per cent of the 38 patients achieving complete relief from symptoms. The BepHan–pHan treated patients, however, approached this high degree of successful response with 79 per cent of the 21 patients reporting freedom from symptoms after 4 to 5 days therapy. A small and equivalent number of patients derived no benefit from either program. A few members of each group experienced return of discomfort when converted to the simpler BepHan schedule. The great majority of patients in both groups, however, remained symptom-free for the duration of the observation period when subsequently treated with only 3 to 4 tablets of BepHan daily. From the patient's standpoint, the effective relief from symptoms as well as improvement in clinical status achieved by the simplified administration and reduced number of tablets met with popular acceptance. The average time the patient received BepHan therapy was 3 weeks, with the longest period of treatment being 2 months.

Early morning gastric aspirations were measured for titrable acidity in 31 patients. Samples were taken before initiating treatment, during the intensive therapy with the modified Sippy regimen or when BepHan and pHan were used for initial therapy. In a group of 19 patients the changes in the gastric

*Calcium carbonate, 0.6 gm., hourly from 7 a.m. to 8 p.m. supplemented by 3 ounces milk and cream hourly 7:30 a.m. to 8:30 p.m.; magnesium oxide tabs. (in place of calcium carbonate) four times a day; and tincture belladonna, 0.5 ml., three times a day.

†pHan® tablets (Sandoz) are composed of 450 mg. of aluminum hydroxide and glycine and 60 mg. of magnesium oxide.

TABLE II

COMPARISON OF AVERAGE CHANGES IN GASTRIC ACIDITY WITH MODIFIED SIPPY, BEPHAN-PHAN AND BEPHAN SPACETABS THERAPY

Treatment	Number of patients	Total Acid						Free HCl					
		Decrease (aver.)			Increase (aver.)			Decrease (aver.)			Increase (aver.)		
		Number of patients	Units	Per cent	Number of patients	Units	Per cent	Number of patients	Units	Per cent	Number of patients	Units	Per cent
Modified Sippy	6	5	22.6	57.2	1	5	12	5	21.8	53.1	1	4	14
BepHan-pHan	11	8	29	59.5	3	15.3	120	7†	30.8	89.1	1†	9	66
BepHan*	19	12	20.6	47	6‡	10	43	16	13.5	62	3	8.3	83.3

*The changes in gastric acidity for the 19 patients treated with BepHan Spacetabs only were compared with the measurements made during prior treatment with modified Sippy.

†3 BepHan-pHan treated patients had no free HCl.

‡One BepHan treated patient showed no change after treatment in total acid.

acidity after 4 to 5 days therapy with BepHan Spacetabs were compared with the results obtained during prior modified Sippy treatment. Table II shows that the use of the modified Sippy program decreased total acid an average of 57.2 per cent and free acid 53.1 per cent in 5 of 6 patients. By comparison, the use of BepHan Spacetabs and pHan tablets initially in 11 patients decreased total acid an average of 59.5 per cent and free acid 89.1 per cent in 8 patients. Three patients, however, showed an increase in total acid and 1 an increase in free acid during therapy. Of some interest are the results (Table II) for the 19 patients continued on only 3 to 4 BepHan Spacetabs daily after 5 to 7 days' intensive treatment with modified Sippy. Twelve of these patients showed a further drop in total acid of an average of 47 per cent and 16 patients registered a 62 per cent decrease in free acid. Six patients, however, showed an average increase of total acid of 43 per cent and 3 an average increase in total acid of 83.3 per cent. Since the acid determinations were all made following the noc-

TABLE III

SIDE-EFFECTS IN 25 PATIENTS DURING BEPHAN THERAPY

Complaint	No. of patients
Constipation	18
Dryness of mouth	2
Urinary retention	1
Blurred vision	1
Nausea	1
Mental disturbance	2

turnal fast, during which no food or drugs were administered, these findings would support the long-acting design of the BepHan Spacetabs.

Side-effects:—Minor side-effects attributed to drug therapy were observed in 25 patients during BepHan therapy (Table III). The most troublesome complaint was constipation, occurring in 18 patients. Since there was no correlation between dosage and constipation, other factors such as age and hospital inactivity may have played a part in contributing to this difficulty. Two patients, a 60-year old woman and an 80-year old man, became mentally disturbed on the third day of BepHan therapy. In both patients the symptoms cleared promptly following discontinuance of therapy. Our feeling was that these reactions were either caused by sensitivity to the anticholinergic agent or, more likely, to the confusional state that is occasionally seen when acutely ill, elderly patients are hospitalized. The other side-effects complained of, such as blurred vision, urinary retention and oral dryness, occurred when the larger dosage of 4 or more BepHan tablets were given daily.

Comment

We feel that any peptic disorder serious enough to require hospitalization should be treated vigorously during the acute phase, consequently, we did not attempt to employ BepHan Spacetabs as the sole therapeutic agent until after from 5 to 7 days of intensive therapy. While BepHan Spacetabs alone in the early therapy may have proved as effective as the more intensive programs we used, it was quite apparent that this preparation could successfully supplant the hourly antacid (calcium carbonate or pHan) and the milk and cream regimens after control of the acute phase. The ability of BepHan to control symptoms with less frequent medication would seem to confirm the sustained therapeutic effect of this formulation. Further, the significant reduction in early morning gastric acidity of patients treated with BepHan, as compared with those treated with the standard neutralizing agents, would support this extended action thesis. In our opinion, BepHan Spacetabs provide an effective and convenient means for continuing long-term treatment in the peptic diseases after an initial period of intensive "suppresive" therapy.

Summary

The BepHan Spacetab represents a pharmaceutical improvement over other similar preparations by combining aluminum hydroxide, glycine, magnesium oxide and bellafoline into one tablet. Pharmacologically, bellafoline (containing the total levorotatory alkaloids of *Atropa Belladonna*) provides a more prolonged anticholinergic effect than belladonna alone. Our findings, based on a study of 59 patients, support the thesis that sustained activity can be accomplished clinically by the use of the BepHan Spacetab in the therapy of a variety of peptic disorders. Compared with initial intensive therapy with a modified Sippy regimen and belladonna, the use of 3 to 4 BepHan Spacetabs supplemented by hourly pHan was found to be nearly as effective as the former on a symptomatic basis. When both forms of intensive therapy were evaluated by the changes in gastric acidity, both regimens were about equally effective. The prolonged effectiveness of the BepHan Spacetab was further demonstrated when it was used alone following initial modified Sippy treatment and a further decrease in gastric acidity resulted. The best response was obtained when 1 BepHan Spacetab, thoroughly chewed, was taken with meals and at bedtime. Because of the effective symptomatic control of symptoms achieved by the convenient schedule of administration with a reduced number of daily medications, patient acceptance of this therapy was excellent. BepHan Spacetabs, used under these conditions, proved a useful agent in the long-term therapy of peptic disorders.

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TOPICAL STEROID THERAPY FOR ULCERATIVE COLITIS

Report of Fifty Cases

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Topical steroid therapy for ulcerative colitis has not been in use long, although topical therapy itself has long been used for ulcerative colitis. At one time the surgical procedures of cecostomy and appendicostomy were employed so that antiseptic agents might be administered directly to the inflamed colon. For the past 15 years we have administered topical therapy to those patients with ulcerative colitis limited to the rectum and sigmoid colon. The medication consists of 100,000 units of penicillin and one gram of one of the nonabsorbable sulfa preparations, such as Sulfathalidine† as a retention enema in from 4 to 6 ounces of water and can be administered by the patient himself with an ear bulb syringe. Since we had been using retention enema therapy consisting of penicillin and sulfa preparations, the early reports of the beneficial effects of cortisone retention enemas in ulcerative colitis excited our interest.

Reports by Other Investigators

In 1956, Allodi and Muratori[1] reported the results in nine patients who each were treated with from 25 to 50 mg. of hydrocortisone instilled through the proctoscope. In 1956, Truelove[2] described a method of intrarectal infusion of an alcoholic solution of hydrocortisone by means of a drip set and rubber catheter. Of 21 patients treated, remission ocurred in 14, improvement in 1, and no change in 6 patients; better results were obtained when an aqueous solution of hydrocortisone hemisuccinate was used[3].

Patterson and McGivney[4] were impressed by the rapidity with which clinical remissions and healing as seen by sigmoidoscopic examinations were obtained in 21 patients with chronic ulcerative colitis who were treated by steroids administered rectally. They[5] obtained good results also in 20 patients having factitious proctitis. Schwartz, Brodoff, Cohn, and Spiro[6] stated that a satisfactory response might be expected in those patients with disease of limited involvement and short duration. Truelove and Witts[7] used a controlled technic in 210 patients. One hundred and nine patients treated with cortisone enemas responded better than 101 patients in the control group who received a similar

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but "dummy" preparation. Death and the necessity to perform ileostomy occurred more often in the control group than in those receiving steroid enemas.

Truelove[8], in 1960, reported the results of a comparative study of 120 patients with ulcerative colitis treated with different types of corticosteroid therapy. He found the combination of oral administration of prednisolone with locally applied hydrocortisone hemisuccinate sodium to be the most effective in causing a rapid clinical remission.

The beneficial action of the topically applied corticosteroids seems to be a local one upon the mucosa. Nabarro, Moxham, Wallker, and Slater[9] reported that no absorption occurred when hydrocortisone was used as a suspension of the acetate; hydrocortisone hemisuccinate sodium was absorbed to a slight

TABLE I

AGE OF 50 PATIENTS WITH ULCERATIVE COLITIS WHO RECEIVED TOPICAL STEROID THERAPY

Age of patients, years	Number of patients
0 to 10	2
11 to 20	6
21 to 30	10
31 to 40	10
41 to 50	13
51 to 60	7
61 to 70	1
71 to 80	1
Total	50

extent; whereas, hydrocortisone in the form of free alcohol was to a large extent absorbed. These studies were confirmed by those of Schwartz and associates[10] who, following instillation of cortisol-4-C^{14}, found no appreciable radioactivity in the plasma cortisol fraction.

Whereas a double-blind control study is always advisable in reporting new types of treatment, this technic has already been employed by Truelove[7,8]. We are reporting the results in 50 patients with ulcerative colitis who were treated with retention enemas of methylprednisolone acetate.

TECHNIC OF ADMINISTRATION

Forty mg. of methylprednisolone acetate* is mixed with the desired amount of tap water (from 100 to 250 ml., depending on the extensiveness of the disease) and may be administered with an ear bulb syringe. When the patient

*Depo-medrol, kindly supplied by The Upjohn Company.

has difficulty in retaining the enema, or when the disease extends beyond the sigmoid colon, the enema may be given slowly (in from two to four hours) by continuous drip from an intravenous bottle attached to a urethral catheter in the rectum. From 200 to 300 ml. may be given, to assure that the medication will extend to the ascending colon. Instead of using the rectal drip method, Barron's food pump may be used to deliver the enema at a constant rate.

Every effort is made to enable the patient to retain the enema, for unless the medication is retained, it is ineffectual. In children, taping the buttocks together may help retention. Belladonna and opium suppositories may be given

TABLE II

DURATION OF SYMPTOMS IN 50 PATIENTS WITH ULCERATIVE COLITIS BEFORE RECEIVING TOPICAL STEROID THERAPY

Duration of symptoms		Number of patients
Months	0 to 6	7
	6 to 12	4
	12 to 18	6
	18 to 24	1
Years	2 to 3	5
	3 to 5	8
	5 to 10	12
	10 to 15	4
	15	3
	Total	50

30 minutes before the enema. In addition, 5 mg. of diphenoxylate hydrochloride[11], a new constipating agent, given before the enema, is effective in enabling many patients to retain the enemas.

In all but three of our patients the enemas were retained from four to ten hours, even though the patient had been having from 15 to 20 stools per day.

Additional therapy, recommended for many patients, included a low-residue, high-protein, high-caloric diet, supplemental vitamins, one of the nonabsorbable sulfa preparations, and an anticholinergic agent or Lomotil*[11]. Many patients were given one of the amine oxidase inhibitors (Catron†). Those patients who did not respond to the amine oxidase inhibitors and those who were greatly disturbed by their symptoms (who were unduly agitated because of severe diarrhea) were frequently helped by Librium‡[12].

*Diphenoxylate hydrochloride with atropine sulfate, supplied by G. D. Searle & Co.
†Catron, supplied by Lakeside Laboratories, Inc.
‡Librium, supplied by Hoffmann-La Roche Inc.

Results

Fifty patients, 29 men and 21 women, were treated with retention enemas of methylprednisolone using the technic described. The age distribution of the patients is shown in Table I: 28 of the patients were less than 40 years of age.

The duration of symptoms was longer than 12 months (chronic disease) in 39 of the 50 patients (Table II). Diarrhea was present in all but five patients. Forty-two patients each had at least four loose stools daily, 25 patients each had a minimum of eight loose stools daily, and 15 patients each had 12 or more watery stools daily. Diarrhea was accompanied by rectal bleeding in 30 of the patients.

Twelve patients were toxic with fever and tachycardia. Twenty-three patients had lost weight, the loss averaging 18 pounds; six patients had lost more than 30 pounds and were severely malnourished. Twenty-three patients were

TABLE III

Degree of Involvement in 50 Patients with Ulcerative Colitis Before Receiving Topical Steroid Therapy

Extent of disease	Number of patients
To	
Rectum	15
Sigmoid and descending colon	2
Transverse colon	8
Entire colon	25
Total	50

anemic; five of these had severe anemia (hemoglobin less than 10 gm. per 100 ml. in males, and 8 gm. per 100 ml. in females).

The extent of the disease in our group is shown in Table III. Only 18 patients had the disease limited to the rectum, sigmoid and descending colon. Consequently, these patients did not have minimal ulcerative proctitis, but the majority had extensive involvement of the colon. All of the patients had received previous therapy to which they had not responded.

Evaluation of the early or immediate responses to treatment is presented in Table IV. This early response was after completion of from 1 to 2 weeks of therapy with the retention enemas. An excellent early response was obtained in 39 of 50 patients with a decrease in symptoms and evidence of regression of the ulcerative colitis by proctoscopic examination. A fair or moderate response was observed in eight patients. Three patients, each with extensive involvement of the colon, did not respond to therapy and underwent colectomy.

The topical therapy with cortisone was usually continued nightly for 2 or 3 weeks, and then was discontinued. The patients were asked to resume the retention enemas immediately when there was a sign of flare-up. They were also asked to continue the general measures, including diet, vitamins, one of the sulfa preparations, an anticholinergic drug, and usually Catron, Librium, or a sedative.

A minimum follow-up of six months (average follow-up of 11.4 months) has been obtained in 41 patients who continued medical treatment (3 of the 50 patients were operated upon on the first admission and there was insufficient follow-up on 6 patients). Twenty-seven patients did not have recurrences and continued to improve. Of the 41 patients, 14 did have recurrences of the ulcerative colitis. Of the 14 who had recurrences, 10 patients had extensive involvement of the colon. These 14 patients were again treated with retention enemas

TABLE IV

EARLY RESPONSE OF 50 PATIENTS WITH ULCERATIVE COLITIS TO TOPICAL STEROID TREATMENT (TWO WEEKS)

Extent of disease	Response, number of patients		
	Excellent	Moderate	Poor (operated upon)
To Rectum	11	4	0
Sigmoid and descending colon	2	0	0
Transverse colon	5	2	1
Entire colon	21	2	2
Total	39	8	3

with cortisone, and with the general measures previously noted. Of the 14, five patients, each with extensive disease, did not respond satisfactorily to resumption of the retention enemas, and colectomy was advised. A second course of therapy with retention enemas was not so effective as the first course.

No failures occurred in the groups in which the disease was limited to the rectum and sigmoid and descending colon (Tables IV and V). Seventeen patients, with the disease so limited, responded satisfactorily on the initial course of therapy. Of 15 in the group with the disease limited to the rectum and descending colon recurrence developed in four patients who responded well to a second course of therapy. None in the group with limited disease required surgery.

In contrast, of the group of 25 patients in which the entire colon was involved, two did not respond to medical therapy initially and required surgery. Of the 21 patients in whom the entire colon was involved, active ulcerative

colitis recurred in seven; a second course of therapy was ineffective in four of those seven patients, and each required colectomy. It is apparent that topical therapy with cortisone is most effective in those with the disease limited to the rectum, sigmoid, and descending colon; and is less effective when there is extensive involvement of the colon. (Two of 21 such patients required colectomy initially and had not responded to medical treatment.)

Case Reports

Case 1:—A 46-year old salesmanager was admitted to the Cleveland Clinic Hospital on 9 January 1960, with ulcerative colitis of 16 years' duration. He had had five toxic episodes with temperature to 104°F. For the previous month he had been having six watery, bloody stools per day. He had received seven blood

TABLE V

Status at Follow-up (Minimum 6 Months) of 46 Patients with Ulcerative Colitis Who Were Treated with Topical Steroid Therapy

Extent of disease	Status, number of patients		
	No recurrence	Recurrence	Required surgery
Rectum	10	3	0
Sigmoid and descending colon	1	1	0
Transverse colon	2	3	1
Entire colon	14	7	4
Total	27	14	5

transfusions in the previous six months. Previous therapy had consisted of corticosteroids orally, vitamins, anticholinergic drugs, and blood transfusions.

The significant laboratory findings were: hemoglobin, 12.3 gm. per 100 ml., and leucocyte count, 9,880 per cu. mm. Stool examinations were positive for blood. The serum albumin was 3.0 gm. and globulin, 40 gm. per 100 ml. Proctoscopic examination revealed a granular, friable, edematous mucosa with many small ulcers. Barium enema examination showed evidence of ulcerative colitis with involvement of the entire colon.

Treatment in the hospital consisted of a high-caloric, low-residue diet, vitamins, Azulfidine*, ACTHar gel† (20 units daily), Lomotil, and Catron. He received retention enemas at bedtime containing 40 mg. of methylprednisolone. He was discharged eight days after admission at which time he was having only 1 or 2 formed stools per day.

*Salicylazosulfapyridine, Pharmacia Laboratories Inc.
†ACTH gel, Armour Pharmaceutical Company.

Subsequently his progress has continued to be excellent with no recurrence of the diarrhea or rectal bleeding. Nine months after he was first treated he was asymptomatic. At that time the hemoglobin was 15 gm. per 100 ml.; serum albumin, 3.68 gm., and serum globulin, 2.52 gm. per 100 ml. Proctoscopic examination disclosed no active ulceration or inflammation. Barium enema examination revealed improvement with an early return of haustral markings in the colon.

Comment:—This patient had had 5 toxic episodes, and was chronically ill requiring frequent transfusions. This patient did not realize how chronically ill

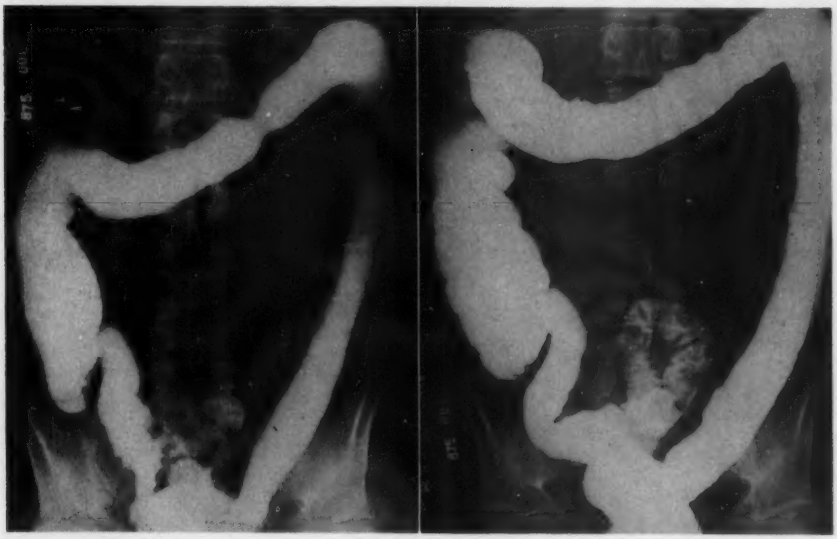

Fig. 1a Fig. 1b

Fig. 1a—Case 1. Barium enema examination of the colon, 6 January 1960. There are no haustral markings, and there is a fuzziness of the margins of the colon indicating minute ulcerations.

Fig. 1b—Progress examination of the colon, 30 August 1960, showing a sharper outline of the margins of the colon indicating that the ulcerations have healed. In addition, there is a suggestion of a return of haustral markings.

he was until he noted the improvement on adequate treatment, including Depo-medrol retention enemas.

Case 2:—An 18-year old girl was referred to the Cleveland Clinic primarily for colectomy and was admitted to the Cleveland Clinic Hospital on 23 June 1960. She had been kept out of school for the previous year because of bloody diarrhea, loss of 30 pounds in weight, and generalized malaise. Physical examination revealed an emaciated young woman who weighed 97 pounds, was 65 inches tall, and who had a temperature of 102°F. The significant laboratory

findings were: hemoglobin, 10.8 gm. per 100 ml., and leucocyte count, 13,500 per cu. mm. with a normal differential smear. Repeated stool examinations showed blood and pus but no parasites. The serum albumin was 2.64 gm., and serum globulin, 3.71 gm. per 100 ml. Proctoscopic examination revealed severe inflammation with thickened valve edges, friability, and bleeding. Barium enema examination showed involvement of the entire colon with ulcerative colitis and pseudopolyposis.

Intensive therapy as previously outlined was instituted, including retention enemas of 40 mg. of methylprednisolone acetate each night. She responded

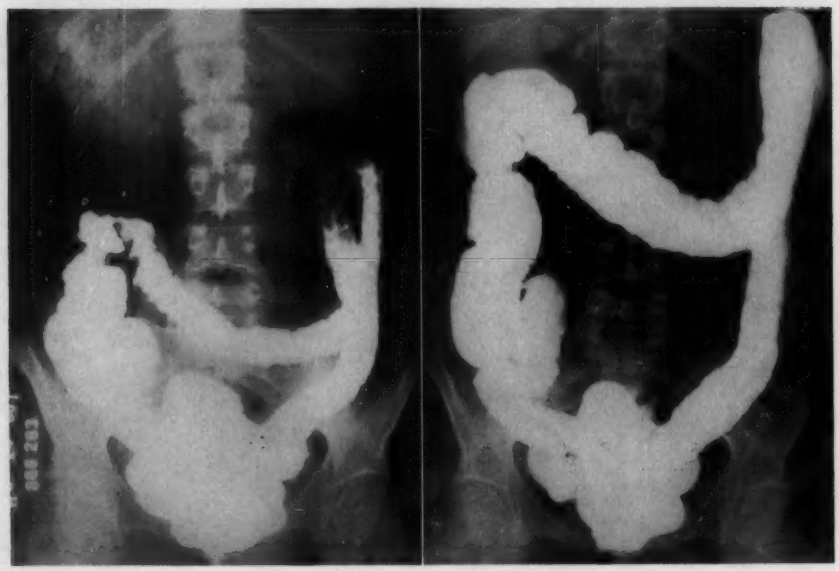

Fig. 2a Fig. 2b

Fig. 2a—Case 2. Barium enema examination of the colon, 24 June 1960, showing a fuzziness of the margins of the colon indicative of ulcerations.
Fig. 2b—Progress examination shows improvement, with no evidence of ulceration and some return of haustral markings.

promptly to therapy with a return of the temperature to normal, cessation of diarrhea, increase in appetite, and a gain in weight. She was asymptomatic when discharged 15 days after admission. Further therapy included dexamethasone, 0.75 mg. twice daily, Azulfidine, one gm. four times daily, Lomotil, 2.5 mg. four times daily, and supplemental vitamins.

On examination on 16 November 1960, the patient still was asymptomatic and had no recurrence of diarrhea. She had gained 42 pounds in weight in

the five months, and had been working eight hours a day. Proctoscopic examination at that time showed some thickening of the valve edge and some scarring of the mucosa but no active ulceration or inflammation. Barium enema examination showed no active ulceration, and a partial return of the haustral markings.

Comment:—This patient, ill with ulcerative colitis for one year, had not responded to previous therapy and was referred to us for surgery. More intensive medical therapy including the use of steroid retention enemas resulted in a remission. She had regained her health without requiring colectomy.

Fig. 3a Fig. 3b

Fig. 3a—Case 2. Snapshot of patient just before admission to the hospital in June, 1960. At that time she weighed 95 pounds and, as can be seen, was severely malnourished.

Fig. 3b—Photograph of patient on 16 November 1960, after she had received treatment for 5 months. In that time, she had gained 42 pounds, was working 8 hours a day, and was asymptomatic and had no diarrhea.

Case 3:—A 20-year old man was admitted to the Cleveland Clinic Hospital on 9 July 1959. He had been chronically ill with ulcerative colitis for seven years and had an acute flare-up of the disease one month before admission. He was having from 15 to 20 liquid, bloody stools per day. He had lost his appetite and 15 pounds in weight, which had dropped to 96 pounds. Proctoscopic examination showed an ulcerated, inflamed, and granular mucosa that bled copiously.

The significant laboratory findings were: hemoglobin, 10.0 gm. per 100 ml., and leucocyte count, 9,880 per cu. mm. Stool examinations were positive for

blood and pus. The serum albumin was 1.56 gm. and serum globulin, 3.94 gm. per 100 ml.

Treatment in the hospital consisted of retention enema of 40 mg. of methylprednisolone acetate, Azulfidine, Lomotil, Catron, and vitamins. At the time of discharge from the hospital his appetite had improved, he was gaining weight, and he was having 3 or 4 formed stools per day without any blood. He was discharged 18 days after admission.

Since discharge from the hospital, the patient has continued to improve and has had no recurrence of diarrhea. When seen on 7 July 1960 (one year after his hospitalization) he had gained 69 pounds in weight. He was having only one formed stool per day without any bleeding. The hemoglobin was 16.2 gm. per 100 ml. The serum albumin was 3.76 gm. and serum globulin, 3.15 gm. per 100 ml. Proctoscopic examination showed no evidence of active ulcerations or inflammation, but there was some scarring and loss of the valve edges. Barium enema examination of the colon revealed rapid filling and some narrowing of all portions except the ascending colon; there was no evidence of active ulcerations.

Comment:—This 20-year man who had been chronically and continuously ill with ulcerative colitis for seven years (since age 13) had not responded to previous therapy. More intensive medical therapy, including steroid retention enemas, resulted in a remission that has lasted more than one year. During this time the patient gained 69 pounds.

Case 4:—A 73-year old factory foreman was admitted to the Cleveland Clinic Hospital on 23 March 1959, from another hospital because of severe diarrhea (20 to 30 watery stools per day) for the previous month. On 12 February the patient contracted influenza for which he received a course of antibiotics. Diarrhea developed approximately three weeks later. The significant laboratory findings were: hemoglobin, 16 gm. per 100 ml., and leucocyte count, 18,000 per cu. mm. The stool examinations were positive for occult blood and showed *Candida albicans*. Proctoscopic examination revealed massive edema and many pseudopolyps of the mucosa. A biopsy specimen of the rectal mucosa revealed extensive infiltration by chronic inflammatory cells. Results of a barium enema examination of the colon were normal.

Medical treatment in the hospital consisted of retention enemas of 40 mg. of methylprednisolone acetate, Azulfidine, Lomotil, and vitamins. The diarrhea promptly subsided. Proctoscopic examination eight days after initiation of therapy showed a disappearance of the previous massive edema. The mucosa was pitted and granular but not actively inflamed. The patient was discharged 10 days after admission.

Proctoscopic examinations, six and 12 months after hospital admission, were normal with no evidence of ulcerative colitis. The patient has remained asymptomatic and has had no recurrence of diarrhea.

Comment:—We believe that this patient's diarrhea, associated with edema and inflammation of the rectal mucosa, may have been caused by the extensive antibiotic therapy administered for influenza. *Candida albicans* was present in the stool. He had not responded to therapy for three weeks in another hospital, continuing to have from 20 to 30 liquid stools daily. Retention enemas of steroids appeared to be particularly efficacious in this patient.

Comment

We have not observed any systemic effects of the steroids administered in the retention enemas. We have used such therapy in patients with diabetes and in two patients with peptic ulcer, without any flare-up in either condition. None of the patients developed "moon face", salt retention, peptic ulcer, or other complications of steroid therapy. Retention enemas of cortisone may be particularly indicated in the patient with ulcerative colitis who has some contraindication to oral or parenteral steroid therapy (diabetes, ulcer).

Patterson[13] pointed out the extreme variations in the topical action of different steroid preparations. He believed that some poor results obtained with this type of therapy in ulcerative colitis had been due to the use of steroids that were ineffective topically.

Topical steroid therapy undoubtedly is not effective in every patient with ulcerative colitis, particularly when there is involvement of the entire colon. Many of our patients had not responded to previous therapy that included all other measures except the retention enemas which resulted in dramatic results.

Hemorrhage and perforation have been reportd as complications of oral or parenteral steroid therapy in patients with ulcerative colitis. The possibility of such complications may be lessened by the concomitant administration of one of the nonabsorbable sulfa preparations such as Sulfathalidine, Azulfidine, or Azudimidine. We have not observed the complications of hemorrhage or perforation in patients given steroids topically. Nonetheless, we believe that patients given topically administered steroid therapy should also be given one of the sulfa preparations as well. Other measures such as diet, supplemental vitamins, anticholinergic drugs and antidiarrheal agents (Lomotil), amine-oxidase inhibitors (Catron), tranquilizers (Librium), or sedative should also be given to these patients as indicated.

Summary

The technic of topical therapy in ulcerative colitis, including retention enemas of penicillin and sulfa preparations and also of cortisone is described. Every effort is made to enable the patient to retain such enemas, including taping the buttocks together in children, belladonna and opium suppositories, anticholinergic drugs and the use of Lomotil.

Retention enemas of 40 mg. of methylprednisolone were given to 50 patients with ulcerative colitis. The immediate response to such treatment (within 2 weeks) was excellent in 39, fair or moderate in 8, and poor in 3 who required colectomy.

Follow-up studies (minimum—6 months, average—11.4 months) in 41 patients showed no recurrence in 27, while 14 had had a flare-up and recurrence of active ulcerative colitis. Five of the 14 who suffered relapses did not respond to further medical therapy and required surgery. A second course of local steroid therapy was less effective than the first course. Eight failures occurred in patients with extensive disease (i.e., involvement of the entire colon). There was an excellent response to therapy in all patients whose disease was limited to the rectum and descending colon.

No systemic effects of the steroids administered in the retention enemas were observed, and the beneficial effect appears to be a local one.

The results of topical steroid therapy in ulcerative colitis are encouraging and merit further use, particularly when the disease is limited.

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President's Message

The excellent program for the Convention and Postgraduate Course which Dr. Robert R. Bartunek and his committee have arranged, merits our sincere thanks. This, however, is not sufficient to repay these hard-working men for the time and effort spent on our behalf. We must, each of us, show our appreciation by attending the sessions and by our presence at the meeting in Cleveland let them know that we realize that they have done their best for us.

The Round Table Discussions on Tuesday, under the guidance of Dr. Stanley S. Sidenberg, Governor of the College for Ohio, promise to be of inestimable value to those seeking knowledge on specific subjects. Here will be an opportunity to discuss problems with experts in each subject.

All day Wednesday is being devoted to the subject of Liver Disease. The speakers at the Symposium and the individual papers being presented will leave very little unsaid in this field.

For those taking the Postgraduate Course, the final session on Saturday afternoon will be an unusual and informative one. The X-ray Classroom with answers to prepared questions and instructional demonstrations should be something worth attending.

Our thanks again to all who helped arrange these fine sessions, exhibits, luncheons, etc. Last of all, we remind you that the Cleveland Chapter will be your hosts at a hospitality room. Check the Hotel Bulletin Board for further information.

See you all in Cleveland!

Henry Baker

NEWS NOTES

Twenty-sixth Annual Convention

This October the Twenty-sixth Scientific Session of the College will be held in Cleveland, Ohio, and it will be the first time that we have met in this city.

The usual committee meetings will be held on Saturday, 21 October 1961. The Board of Trustees will hold its Annual Meeting on Sunday, 22 October 1961 and will then join the Board of Governors in a joint luncheon. On Sunday afternoon, the Annual Meeting of the Fellows of the College will take place, at which time Officers, Trustees and Governors are to be elected. There will also be some amendments to the By-laws to be acted upon.

Mrs. William W. Abrams, President of the Women's Auxiliary will preside at their Annual Meeting which will also be held on Sunday afternoon. The Convention Chairman, Mrs. Maxwell Berry and her very capable Program Committee, headed by Mrs. Harman Shecket, have carefully arranged the activities for the week.

Our Annual Convocation Ceremony will be held in the Main Ballroom at the Sheraton-Cleveland, on Sunday evening, at 6:30 P.M. Certificates will be presented to the newly elected and advanced Fellows and Associate Fellows and to Dr. Charles H. Brown of Cleveland, Honorary Fellow.

William H. Rorer, Inc. of Philadelphia, Pa. will again be our hosts at the Buffet Supper at 8:30 P.M., following the Convocation. Admission is by card only and these may be obtained at the Convocation Ceremony.

Each morning, Monday through Thursday, Wyeth Laboratories of Philadelphia, Pa. will serve coffee and sweet rolls in the Exhibit Area, from 8:30 to 9:30.

Dr. Henry Baker of Boston, Mass., President of the College will open the Scientific Session at 9:00 A.M. on Monday morning, 23 October 1961. Sessions will be held at the hotel on Tuesday and Wednesday as well, with papers being presented on topics of vital interest in gastroenterology and allied fields. There will be several innovations in the program this year. On Tuesday afternoon, 24 October 1961 the entire session will consist of a series of Round Table Discussions. There will be 20 such Tables to which those attending can go and spend as much or as little time. There will be three "experts" at each table to conduct the discussion. The entire day on Wednesday, 25 October 1961 will be devoted to papers on Liver Disease with a Symposium on the subject commencing 9:00 A.M. and ending 3:20 P.M. Carefully selected technical and scientific exhibits will be located in the rooms leading to the Ballroom.

The Registration Desk will be on the Ballroom floor and will be open from 1:00 P.M. to 4:30 P.M. on Sunday and each day thereafter from 8:30 A.M. to 4:30 P.M.

Our hosts at their Annual Luncheon on Monday, 23 October 1961, will again be Burton, Parsons & Co., Washington, D.C. An outstanding speaker has been obtained and tickets for this luncheon are available upon request at the Registration Desk.

The Annual Meeting of the Board of Governors has been changed to a breakfast session at 7:30 A.M. on Tuesday, 24 October 1961, to permit a special briefing luncheon for those participating in the Round Table Discussions.

Tickets for our Annual Dinner-Dance will again be available by tables and those desiring to sit together are urged to purchase their tickets at the same time. Silver Certificates, signifying 25 years of affiliation will again be presented.

The retiring President, Dr. Baker will install our President-elect, Dr. Louis Ochs, Jr., of New Orleans, La. and turn over to him the insignia of office.

A program of music, dancing and entertainment has been planned for the evening.

A special luncheon meeting for the newly elected Board of Trustees will take place on Wednesday, 25 October 1961.

The Committee for this year's Scientific Program and Course in Postgraduate Gastroenterology was headed by Dr. Robert R. Bartunek of Cleveland, Ohio. The other members of his committee were: Dr. Henry A. Monat, Washington, D.C.; Dr. Stanley S. Sidenberg, Cleveland, Ohio; Dr. Edward J. Krol, Chicago, Ill.; Dr. David A. Dreiling, New York, N. Y. and Dr. Lynn A. Ferguson, Grand Rapids, Mich.

The tentative program appears in this issue and the final copies will be mailed to those affiliated with the College. Others desiring to obtain copies may write to the headquarters office, 33 West 60th St., New York 23, N. Y.

Scientific Exhibits

Scientific Exhibits will be on display on the Ballroom floor from Monday morning, 23 October 1961 through noon on Thursday, 26 October 1961. The Scientific Exhibit Committee is composed of Dr. Lester M. Morrison, Los Angeles, Calif., Chairman; Dr. Fredrick Steigmann, Chicago, Ill. and Dr. Joseph E. Walther, Indianapolis, Ind. Certificates and ribbons will be awarded to those exhibits which, in the opinion of the Committee, merit their receipt.

Course in Postgraduate Gastroenterology

This year our Annual Course in Postgraduate Gastroenterology, which follows the Convention, will be held, not only at the Sheraton-Cleveland, but there will also be two outside sessions. The first of these will be on Thursday afternoon, 26 October 1961, at the Frank E. Bunts Educational Institute of the Cleve-

land Clinic. The second will be on Friday evening, 27 October 1961 and will be a joint meeting with the Cleveland Academy of Medicine at the Academy Building. The speaker on Friday evening will be Dr. H. Marvin Pollard of Ann Arbor, Mich.

The Course, which commences on Thursday morning, will continue until Saturday afternoon. There will be another evening session on Thursday to which those who have registered for the Annual Convention will be admitted. At all other times attendance is limited to those who have registered and paid the matriculation fee.

The final session of the Course on Saturday afternoon, 28 October 1961 will consist of an X-ray Classroom. There will be prepared questions and answers with instructional demonstrations. Audience participation will be permitted if time allows.

The Postgraduate Course, planned in cooperation with the Ohio State Academy of General Practice, has been granted 17 hours of Category I credit for training, by the Ohio State Academy of General Practice.

Nominating Committee Report

The Nominating Committee of the College, consisting of Dr. Joseph Shaiken, Milwaukee, Wisc., Chairman; Dr. Louis Ochs, Jr., New Orleans, La.; Dr. Stanley S. Sidenberg, Cleveland, Ohio; Dr. Robert T. McCarty, Milwaukee, Wisc. and Dr. John F. Keane, Brookline, Mass., has submitted the following slate of candidates to be voted upon at the Annual Meeting of the Fellowship, on Sunday, 22 October 1961:

Officers

President-elect	Edward J. Krol, M.D., Chicago, Ill.
1st Vice-President	Theodore S. Heineken, M.D., Glen Ridge, N. J.
2nd Vice-President	Donald C. Collins, M.D., Hollywood, Calif.
3rd Vice-President	Robert R. Bartunek, M.D., Cleveland, Ohio
4th Vice-President	Milton J. Matzner, M.D., Brooklyn, N. Y.
Secretary-General	Lynn A. Ferguson, M.D., Grand Rapids, Mich.
Secretary	Louis L. Perkel, M.D., Jersey City, N. J.
Treasurer	William C. Jacobson, M.D., New York, N. Y.

Board of Trustees

For 3 years:	Harry Barowsky, M.D., New York, N. Y.
	Maxwell Berry, M.D., Atlanta, Ga.
	S. Bernard Kaplan, M.D., Newark, N. J.
	Charles W. McClure, M.D., Cambridge, Mass.
	Harold Messenger, M.D., San Diego, Calif.

Board of Governors

For 3 years:	
Florida	Fred E. Manulis, M.D., Palm Beach
Illinois	George J. Rukstinat, M.D., Chicago
Indiana	Joseph E. Walther, M.D., Indianapolis
Iowa	Elwood Buchman, M.D., Iowa City
Louisiana	William Fisher, M.D., New Orleans
Lower New York	Edward J. Nightingale, M.D., New York City
Ohio	Stanley S. Sidenberg, M.D., Cleveland
Rhode Island	William L. Leet, M.D., Providence
Texas	H. B. Eisenstadt, M.D., Port Arthur
West Virginia	Emil Gribovsky, M.D., Huntington
Quebec	Paul Letendre, M.D., Montreal
For 2 years:	
Massachusetts	John F. Keane, M.D., Brookline

WOMEN'S AUXILIARY PROGRAM

The program for the Women's Auxiliary has been capably arranged by the Convention Chairman, Mrs. Maxwell Berry of Atlanta, Georgia and a Program Committee in Cleveland, whose Chairman is Mrs. Harman A. Shecket.

Sunday, 22 October 1961

The Registration Desk will open at 12:00 noon at the Sheraton-Cleveland. Ladies are urged to make reservations and purchase tickets for the various activities in advance.

The Annual Meeting of the Auxiliary, for the election and intsallation of offices, takes place at 2:00 P.M. Tea will be served at 3:30 P.M.

A color movie, with sound, of Cleveland and its role in the St. Lawrence Seaway will be shown following the tea.

The Convocation Ceremony of the College will take place in the Main Ballroom at 6:30 P.M. and the ladies are invited to attend. A buffet supper will follow at 8:30 P.M.

Monday, 23 October 1961

The Registration Desk will be open at 8:30 A.M.

At 9:15 A.M. buses will leave the Hotel for a sightseeing tour of the city. At 1:00 P.M. there will be a luncheon at the Cleveland Play House Club fol-

lowed by a visit behind the scenes at the Cleveland Play House, to watch the rehearsal of a play in production. Return to the hotel will be by bus.

Tuesday, 24 October 1961

The Registration Desk will be open at 8:30 A.M.

At 9:15 A.M. buses will leave for the General Electric Lighting Institute at Nela Park "Light for Living Center". This will be followed by a luncheon and Style Show at the Cleveland Skating Club. The show will be arranged through the courtesy of the Hathaway Shaker Square Women's Apparel Shop.

After lunch the group will be able to visit the Shaker Square Shopping Area, a few blocks from the Skating Club. For those who wish to have their hair fixed for the Banquet, the Committee will have a list of beauty shops available.

Return to the Hotel will be by Rapid Transit cars which leave Shaker Square at approximately 10-minute intervals for the downtown terminal. The Sheraton-Cleveland can be reached by a direct passageway from the terminal. In the event of rain there will be buses from the Skating Club back to the Hotel.

At 7:00 P.M. the College will have its Annual Dinner-Dance preceded by cocktails. This will be at the Sheraton-Cleveland and will feature dancing and entertainment. Dress will be informal.

Wednesday, 25 October 1961

The Registration Desk will be open at 8:30 A.M.

The newly elected officers will conduct a business meeting at 10:00 A.M.

Tickets will be available for a matinee performance of *Advise and Consent* at the Hanna Theatre. Choice orchestra seats will be available.

For those who do not care to attend the theatre, a trip has been arranged to the Cleveland Museum of Art, the Cleveland Museum of Natural History and the Snow Planetarium.

Reservations for all of the above activities are required and should be made in advance.

26th ANNUAL CONVENTION
AMERICAN COLLEGE OF GASTROENTEROLOGY

Sheraton-Cleveland
Cleveland, Ohio
22-25 October 1961

The Cleveland Chapter of the American College of Gastroenterology guarantees you, regardless of the weather outside, a warm glow in their hospitality rooms at the Sheraton-Cleveland.

Plan to meet your fellow members there! Consult the hotel Bulletin Board on your arrival.

PRELIMINARY PROGRAM

TWENTY-SIXTH ANNUAL CONVENTION AMERICAN COLLEGE OF GASTROENTEROLOGY

SCIENTIFIC SESSIONS 23, 24, 25 OCTOBER 1961

AND

COURSE IN POSTGRADUATE GASTROENTEROLOGY 26, 27, 28 OCTOBER 1961

SHERATON-CLEVELAND CLEVELAND, OHIO

GENERAL INFORMATION

REGISTRATION—All members and guests should register. Identification badges for admittance to meetings will be given to those who register. These should be worn at all times during the session. Registration will take place at the registration desk on the convention floor. Registration facilities wil lopen at 1:00 P.M. on Sunday and at 8:30 each morning.

LADIES REGISTRATION—At the registration desk on the Convention Floor. Registration facilities will open at 12:00 Noon on Sunday and at 8:30 each morning. Information concerning the various activities and events will be available there.

DINNER-DANCE—Tickets will be sold by tables and will be available at the registration desk. Those desiring to be seated together must purchase tickets at the same time.

MEETINGS are held on local time and will begin promptly at the time specified.

COURSE IN POSTGRADUATE GASTROENTEROLOGY—Admittance only upon presentation of official matriculation card.

SCIENTIFIC EXHIBITS—Will be in the Exhibit Hall and will be open Monday, Tuesday and Wednesday 8:30 A.M. to 5 P.M., Thursday from 8:30 A.M. to 1:00 P.M.

TECHNICAL EXHIBITS under the direction of Mr. Steven K. Herlitz, Exhibit Manager, will be open Monday, Tuesday and Wednesday from 8:30 A.M. to 5:00 P.M., Thursday from 8:30 A.M. to 1:00 P.M.

Those attending the Convention are urged to take advantage of the time in between the presentation of papers and sessions, to visit the technical exhibits and become acquainted with the many new products and new equipment on display.

Business Sessions

SATURDAY, 21 OCTOBER 1961

All Day
Various committee meetings at times to be arranged by committee chairmen—Parlor 34.

SUNDAY, 22 OCTOBER 1961

9:00 A.M.
Annual Meeting of the Board of Trustees—Parlor 34.

1:00 P.M.
Luncheon, Board of Trustees and Board of Governors—Terminal Room.

3:00 P.M.
Annual Meeting of the American College of Gastroenterology—Empire Room.

4:45 P.M.
Convocation Rehearsal (without caps and gowns)—Main Ball Room

6:30 P.M.
CONVOCATION: Presentation of Certificates —Main Ball Room. See special program.

8:30 P.M.
Buffet Supper—Cleveland Room. Sponsored by William H. Rorer, Inc. (Admission by card only, to be obtained at the Convocation Ceremony).

MONDAY, 23 OCTOBER 1961

5:00 P.M.
Meeting of the Credentials Committee—Directors Room.

TUESDAY, 24 OCTOBER 1961

7:30 A.M.
Annual Meeting and Breakfast of the Board of Governors—Directors Room.

WEDNESDAY, 25 OCTOBER 1961

12:30 P.M.
Luncheon Meeting of the Board of Trustees —Directors Room.

SCIENTIFIC SESSIONS

FIRST SESSION

MONDAY MORNING,

23 OCTOBER 1961

8:30–9:30 A.M. *Coffee and sweet rolls will be served in the Exhibit Area.**

HENRY BAKER, M.D., F.A.C.G., President, American College of Gastroenterology, presiding.

9:00 A.M.

1. **Cinefluorographic Diagnosis of Small Hiatal Hernia.**

DR. FRANK L. CAMPETI, Rochester, N. Y. (By invitation) and DR. NATHAN GEFFEN, Rochester, N. Y. (By invitation).

9:20 A.M.

2. **Etiology and Management of Benign Lower Esophageal Obstruction.**

DR. FRANK B. MCGLONE, Denver, Colo. (By invitation) and DR. HENRY JOB, Denver, Colo. (By invitation).

Discussion

DR. WILLIAM E. NEVILLE, Cleveland, Ohio.

9:40 A.M.

3. **Phlegmonous Gastritis.**

DR. LOWELL R. SMITH, El Cajon, Calif. and DR. CHARLES M. GARRETT, La Mesa, Calif. (By invitation).

9:55 A.M.

4. **Massive Gastrointestinal Hemorrhage of Undetermined Origin.**

DR. LEO R. MILNER, Boston, Mass.

10:10 A.M.

5. **Variations of Duodenal Diverticuli; Source of Occult Bleeding.**

DR. MICHAEL M. KLEIN, Huntington, W. Va. (By invitation), DR. ROBERT L. BRADLEY, Huntington, W. Va. (By invitation) and DR. EMIL GRIBOVSKY, Huntington, W. Va.

10:20 A.M. Recess to visit the commercial, technical and scientific exhibits.

10:50 A.M.

6. **Gastric Hypothermia in Upper Gastrointestinal Bleeding.**

DR. ALEXANDER RICHMAN, New York, N. Y. (By invitation) and DR. DONALD ANTHONY, New York, N. Y. (By invitation).

11:10 A.M.

Discussion of Papers 4, 5 and 6.

DR. JOHN M. MCMAHON, Bessemer, Ala.

11:20 A.M.

7. **Gastroscopy and Gastrobiopsy in the Evaluation of Gastric Disease.**

DR. LEONIDAS H. BERRY, Chicago, Ill.

11:35 A.M.

8. **Gastric Tissue Changes in Association with Peptic Ulcer.**

DR. EMMANUEL DEUTSCH, Boston, Mass. (By invitation) and DR. HOWARD J. CHRISTIAN, Boston, Mass. (By invitation).

11:50 A.M.

9. **Cinema Gastrophotography.**

DR. JULIUS WOLF, Bronx, N. Y. (By invitation), DR. HENRY COLCHER, New York, N. Y. and DR. HERBERT B. RADACK, Bronx, N. Y. (By invitation).

12:10 P.M.

Comments: DRS. BERRY, DEUTSCH and WOLF.

Questions on Papers 7, 8 and 9 as time permits.

12:20 P.M. Recess.

12:30 P.M.

LUNCHEON–Sponsored by Burton, Parsons & Co.–Cleveland Room. (Admission by card only, to be obtained at the registration desk.)

*Compliments of Wyeth Laboratories.

SECOND SESSION

MONDAY, AFTERNOON,

23 OCTOBER 1961

EDWARD J. KROL, M.D., F.A.C.G., Vice-President, American College of Gastroenterology, presiding.

2:00 P.M.

10. Drainage of Cholesterol by Choleresis: Clinical Evaluation.

DR. ANGEL RODRIGUEZ OLLEROS, Santurce, P. R.

2:15 P.M.

11. Special Staining Technics and the Clinical Pathology of Cholecystitis.

DR. GEORGE J. RUKSTINAT, Chicago, Ill.

2:30 P.M.

12. Stenosis of Gallbladder Associated with Intramural Diverticulosis.

DR. MILTON J. MATZNER, Brooklyn, N. Y. and DR. IRA TEICHER, Brooklyn, N. Y. (By invitation).

2:45 P.M.

13. Changes in the Gastrointestinal Tract in Dermatomyositis.

DR. JEROME A. ECKER, Santa Barbara, Calif.

3:00 P.M.

14. Evaluation of Tests for Small Intestinal Malabsorption.

DR. HUGO C. MOELLER, San Francisco, Calif. (By invitation) and DR. J. ALFRED RIDER, San Francisco, Calif. (By invitation).

Discussion

DR. HAROLD H. SCUDAMORE, Rochester, Minn.

3:20 P.M. Recess to visit the commercial, technical and scientific exhibits.

3:50 P.M.

15. Thiethylperazine: Postoperative Vomiting (Double-blind Study)—Localization in Central Nervous System by Chemical Extraction and Fluorescent Technics.

DR. ROBERT D. SPARKS, New Orleans, La. (By invitation), DR. DONOVAN C. BROWNE, New Orleans, La., DR. PAUL GUTH, New Orleans, La. (By invitation), DR. VICTOR FERRANS, New Orleans, La. (By invitation) and DR. FRED HUNTER, New Orleans, La. (By invitation).

Discussion

DR. MAXWELL R. BERRY, Atlanta, Ga.

4:10 P.M.

16. The Life History of the Carcinoid Tumor of the Small Intestine.

DR. CHARLES G. MOERTEL, Rochester, Minn. (By invitation), DR. WILLIAM G. SAUER, Rochester, Minn. (By invitation), DR. MALCOLM B. DOCKERTY, Rochester, Minn. (By invitation) and DR. ARCHIE H. BAGGENSTOSS, Rochester, Minn. (By invitation).

4:30 P.M.

17. Cancer Dissemination from the Gastrointestinal Tract.

DR. ALVIN L. WATNE, Buffalo, N. Y. (By invitation) and DR. GEORGE E. MOORE, Buffalo, N. Y. (By invitation).

Discussion

DR. JEROME WEISS, New York, N. Y.

4:50 P.M.

18. Treatment of Flatulent Distention in Ambulatory Patients—A Double-blind Study.

DR. BENJAMIN O. MORRISON, New Orleans, La. and DR. JAMES H. GRANT, New Orleans, La. (By invitation).

5:10 P.M. Recess.

THIRD SESSION

TUESDAY MORNING,

24 OCTOBER 1961

7:30 A.M. Board of Governors Annual Meeting and Breakfast—Directors Room.

8:30–9:30 A.M. *Coffee and sweet rolls will be served in the Exhibit Area.**

THEODORE S. HEINEKEN, M.D., F.A.C.G., Vice-President, American College of Gastroenterology, presiding.

9:00 A.M.

19. Bowel Resection: The Essentials of Pre- and Postoperative Care.

DR. WALTER SHRINER, Springfield, Ill.

Discussion

DR. EARL J. HALLIGAN, Jersey City, N. J.

9:20 A.M.

20. Current Advances in Sigmoidoscopic Technics.

DR. EMIL GRANET, New York, N. Y.

Discussion

DR. JOHN P. WAITKUS, Chicago, Ill.

9:40 A.M.

21. Current Concepts of Staphylococcal Enterocolitis.

DR. JOHN H. DAVIS, Cleveland, Ohio (By invitation).

10:00 A.M.

22. Adenomatous Polyps of the Colon: Pathogenesis and Management.

DR. JACK W. COLE, Cleveland, Ohio (By invitation).

10:20 A.M. Recess to visit the commercial, technical and scientific exhibits.

*Compliments of Wyeth Laboratories.

10:50 A.M.

23. Ulcerative Colitis — Hypersensitivity Disease?

DR. J. ALFRED RIDER, San Francisco, Calif. (By invitation), DR. HUGO C. MOELLER, San Francisco, Calif. (By invitation) and DR. JOHN O. GIBBS, San Francisco, Calif. (By invitation).

Discussion

DR. LOUIS L. PERKEL, Jersey City, N. J.

11:15 A.M.

24. Steroids in the Management of Ulcerative Colitis.

DR. JEAN A. SPENCER, Chicago, Ill. (By invitation) and DR. JOSEPH B. KIRSNER, Chicago, Ill. (By invitation).

Discussion

DR. HAROLD MESSENGER, San Diego, Calif.

11:40 A.M.

25. Prolonged Narcosis in the Treatment of Severe Ulcerative Colitis.

DR. EDWARD O. HARPER, Cleveland, Ohio (By invitation).

Discussion

DR. ARTHUR J. ATKINSON, Chicago, Ill.

12:05 P.M.

26. Factors Affecting Ileostomy Function.

DR. SIDNEY M. FIERST, Brooklyn, N. Y. and DR. ALEXANDER LAZAR, Brooklyn, N. Y. (By invitation).

Discussion

DR. RALPH R. BRAUND, Memphis, Tenn.

FOURTH SESSION

TUESDAY AFTERNOON,

24 OCTOBER 1961

STANLEY S. SIDENBERG, M.D., F.A.C.G., Governor for Ohio, American College of Gastroenterology, presiding.

2:00 P.M. to 3:20 P.M.

27. Round Table Discussions.

Table 1. Esophagus

DR. HAROLD G. KLEIN, Cleveland, Ohio
DR. MILTON J. MATZNER, Brooklyn, N. Y.
DR. FRANK B. MCGLONE, Denver, Colo. (By invitation)

Table 2. Esophagus

DR. LEONIDAS H. BERRY, Chicago, Ill.
DR. EDWIN BOROS, New York, N. Y.
DR. WILLIAM E. NEVILLE, Cleveland, Ohio

Table 3. Ulcer

DR. MAXWELL R. BERRY, Atlanta, Ga.
DR. MAX CAPLAN, Meriden, Conn.
DR. EDWARD A. MARSHALL, Cleveland, Ohio

Table 4. Ulcer

DR. HENRY BAKER, Boston, Mass.
DR. CHARLES W. MCCLURE, Cambridge, Mass.
DR. LOUIS L. PERKEL, Jersey City, N. J.

Table 5. Endocrine Ulcer

DR. MURREL H. KAPLAN, New Orleans, La.
DR. JOSEPH SHAIKEN, Milwaukee, Wisc.
DR. MITCHELL A. SPELLBERG, Chicago, Ill.

Table 6. Functional Gastrointestinal Disease

DR. ARTHUR J. ATKINSON, Chicago, Ill.
DR. LIBBY PULSIFER, Rochester, N. Y.
DR. JOSEPH E. WALTHER, Indianapolis, Ind.

Table 7. Gastrointestinal Hemorrhage

DR. HOWARD M. GANS, Cleveland, Ohio
DR. CHET R. LULENSKI, Cleveland, Ohio (By invitation).
DR. LEO R. MILNER, Boston, Mass.

Table 8. Gastric Surgery

DR. RALPH R. BRAUND, Memphis, Tenn.
DR. HARRY GOLDMAN, Cleveland, Ohio
DR. MILTON M. LIEBERTHAL, Bridgeport,, Conn.

Table 9. Nutrition

DR. SEYMOUR L. HALPERN, New York, N. Y.
DR. HENRY A. MONAT, Washington, D.C.
DR. LESTER M. MORRISON, Los Angeles, Calif.

Table 10. Gallbladder Surgery

DR. JAC S. GELLER, Cleveland, Ohio
DR. JAMES T. NIX, New Orleans, La.
DR. GEORGE J. RUKSTINAT, Chicago, Ill.

Table 11. Pancreas

DR. DALE W. CREEK, Santa Barbara, Calif.
DR. DAVID FISHMAN, Cleveland, Ohio
DR. PAUL L. SHALLENBERGER, Waverly, N. Y.

Table 12. Liver Disease

DR. GEORGE J. GABUZDA, JR., Cleveland, Ohio. (By invitation)
DR. FREDERICK STEIGMANN, Chicago, Ill.
DR. HARMAN A. SHECKET, Cleveland, Ohio

Table 13. Small Intestine (Enteritis)

DR. HEINZ B. EISENSTADT, Port Arthur, Texas
DR. BERTRAM FLESHLER, Cleveland, Ohio (By invitation).
DR. ERWIN LEVIN, Cleveland, Ohio (By invitation).

Table 14. Intestinal Parasites

DR. EMILE GRIBOVSKY, Huntington, W. Va.
DR. MANUEL RODRIGUEZ, Cleveland, Ohio. (By invitation)

Table 15. Colon Disease

DR. DONALD C. COLLINS, Hollywood, Calif.
DR. HAROLD MESSENGER, San Diego, Calif.
DR. JOHN P. WAITKUS, Chicago, Ill.

Table 16. Colon Disease (Diverticulitis)

DR. EARL J. HALLIGAN, Jersey City, N. J.
DR. EDWARD J. KROL, Chicago, Ill.
DR. JOSEPH MC K. ROSSEN, Cleveland, Ohio

Table 17. Proctology

DR. EMIL GRANET, New York, N. Y.
DR. CLAYTON C. PERRY, Cleveland, Ohio (By invitation).
DR. S. FRANK WEINMAN, Cleveland, Ohio (By invitation).

Table 18. New Therapeutic Modalities

DR. I. HENRY EINSEL, Cleveland, Ohio
DR. ALEXANDER RICHMAN, New York, N. Y. (By invitation)
DR. JACOB J. WEINSTEIN, Washington, D.C.

Table 19. Pediatric Gastrointestinal Disease

DR. LEON DEMBO, Cleveland, Ohio. (By invitation)
DR. NORMAN GLAZER, Cleveland, Ohio (By invitation).
DR. ROBERT J. IZANT, JR., Cleveland, Ohio. (By invitation)
DR. JEROME WEISS, New York, N. Y.

Table 20. Colostomy Demonstration (with patients)

DR. HENRY W. BROWN, Cleveland, Ohio
DR. SIDNEY M. FIERST, Brooklyn, N. Y.
DR. WALTER SHRINER, Springfield, Ill.

3:20 P.M. Recess to visit the commercial, technical and scientific exhibits.

3:50 P.M.
Resumption of Round Table Discussions.

5:00 P.M. Recess.

7:00 P.M.

ANNUAL DINNER DANCE — CLEVELAND ROOM, Sheraton-Cleveland Hotel, Cleveland, Ohio.

FIFTH SESSION

WEDNESDAY MORNING,
25 OCTOBER 1961

8:30–9:30 A.M. *Coffee and sweet rolls will be served in the Exhibit Area.**

DONALD C. COLLINS, M.D., F.A.C.G., Vice-President, American College of Gastroenterology, presiding.

9:00 A.M. and all day.

28. Symposium on Liver Disease.

Moderator

DR. FENTON SCHAFFNER, New York, N. Y. (By invitation).

Participants:

Bromsulfalein—DR. DONALD BERKOWITZ, Philadelphia, Pa. (By invitation).

Ascites, Mechanical Removal—DR. RICHARD C. BRITTON, Cleveland, Ohio (By invitation).

Proteins, Ammonia—DR. GEORGE J. GABUZDA, JR., Cleveland, Ohio (By invitation).

Lipids—DR. SOL GLASSMAN, Philadelphia, Pa. (By invitation).

Isotopes—DR. DIETER KOCH-WESER, Cleveland, Ohio (By invitation).

Ascites, Medical Management—DR. M. C. F. LINDERT, Milwaukee, Wisc.

Immunity, Autoagglutinins—DR. LESTER M. MORRISON, Los Angeles, Calif.

Malabsorption—DR. HAROLD H. SCUDAMORE, Rochester, Minn. (By invitation).

Phosphatase, Enzymes—DR. MITCHELL A. SPELLBERG, Chicago, Ill.

Steroids—DR. PAUL L. SHALLENBERGER, Waverly, N. Y.

Toxic Jaundice—DR. HYMAN J. ZIMMERMAN, Chicago, Ill. (By invitation).

10:20 A.M. Recess to visit the commercial, technical and scientific exhibits.

10:50 A.M.
Symposium on Liver Disease (continued).

12:30 P.M. Board of Trustees Special Meeting and Luncheon—Directors Room.

*Compliments of Wyeth Laboratories.

SIXTH SESSION

WEDNESDAY AFTERNOON,

25 OCTOBER 1961

JOSEPH SHAIKEN, M.D., F.A.C.G., Chairman, Board of Trustees, American College of Gastroenterology, presiding.

2:00 P.M.

Symposium on Liver Disease (continued).

3:20 P.M. Recess to visit the commercial, technical and scientific exhibits.

3:50 P.M.

29. Reciprocal Relationship Between Pancreatitis and Liver Disease.

DR. FREDERICK STEIGMANN, Chicago, Ill., DR. PAUL SZANTO, Chicago, Ill. (By invitation) and DR. K. CHUNG, Chicago, Ill. (By invitation).

4:10 P.M.

30. The Liver in Heart Disease.

DR. SALVATORE M. SANCETTA, Cleveland, Ohio (By invitation).

4:30 P.M.

31. Hypertension and Liver Disease.

DR. HUBERT F. LOYKE, Cleveland, Ohio (By invitation).

The following papers will be read by title only:

32. The Ulcer Diet—Attention to Saturated and Polyunsaturated Fatty Acids.

DR. DAVID J. SANDWEISS, Detroit, Mich.

33. Factors in Successful Treatment of Duodenal Ulcer.

DR. HENRY A. MONAT, Washington, D.C.

34. Ulcers and Gallbladder Disease in Children.

DR. JEROME WEISS, New York, N. Y., DR. SAMUEL WEISS, New York, N. Y. and DR. BERNARD WEISS, New York, N. Y. (By invitation).

35. An Experiment on Carbon Dioxide Therapy.

DR. ARTHUR J. ATKINSON, Chicago, Ill. and DR. GEORGE K. YACORZYNSKI, Chicago, Ill. (By invitation).

36. Aldosterone Antagonist and a Thiazide Diuretic in the Treatment of Cirrhosis with Ascites.

DR. M. C. F. LINDERT, Milwaukee, Wisc., DR. JACK J. LEVIN, Wood, Wisc. and DR. D. A. ROTH, Milwaukee, Wisc. (By invitation).

37. Replacement of Strictural or Carcinomatous Bile Ducts with a Gastric Pedicle Tube.

DR. HENRY J. HEIMLICH, New Rochelle, N. Y. and DR. GEORGE GITLITZ, New Rochelle, N. Y. (By invitation).

38. The Disaster of Failing to Recognize that Acute Appendicitis may be Caused by Left-sided Colonic Lesions of Major Importance.

DR. DONALD C. COLLINS, Hollywood, Calif.

39. Clinical Evaluation of Cellulase with Other Enzymes in Treatment of Digestive Disorders.

DR. A. RAY HUFFORD, Grand Rapids, Mich.

40. Weight Loss Without Trauma.

DR. SEYMOUR LIONEL HALPERN, New York, N. Y.

41. Thirty Years' Experience with Psychiatric Needs of Patients.

DR. L. PULSIFIER, Rochester, N. Y.

42. Use of the Much-Maligned Whitehead Operation for Hemorrhoids.

DR. EDWARD F. SCIORSCI, Hoboken, N. J.

COURSE IN POSTGRADUATE GASTROENTEROLOGY

FIRST SESSION

THURSDAY MORNING,
26 OCTOBER 1961

Attendance at the Postgraduate Course is limited to those who have registered and paid the matriculation fee.

8:30 A.M.–9:30 A.M. *Coffee and sweet rolls will be served in the Exhibit Area.**

8:50 A.M.

Address of Welcome–LOUIS OCHS, JR., M.D., F.A.C.G., President, American College of Gastroenterology.

9:00 A.M.

1. **Pathophysiology of Pancreatic Inflammation.**
   DR. DAVID A. DREILING, New York, N. Y.
2. **The Laboratory Diagnosis of Pancreatic Disease.**
   DR. HENRY D. JANOWITZ, New York, N. Y.
3. **Medical Therapy of Pancreatitis.**
   DR. MURREL H. KAPLAN, New Orleans, La.

10:15 A.M. Recess to visit the commercial, technical and scientific exhibits. (Exhibits close at 12:30 P.M.).

10:45 A.M.

4. **Surgical Management of Pancreatic Inflammation.**
   DR. MERLIN K. DUVAL, JR., Oklahoma City, Okla.
5. **Surgical Management of Pancreatic Tumefactions.**
   DR. EDWIN H. ELLISON, Milwaukee, Wisc.

11:40 A.M.

Question and Answer Period.
DRS. DREILING *(Moderator)*, DUVAL, ELLISON, JANOWITZ and KAPLAN.

a. From Question Box
b. Audience Participation

12:15 P.M. Recess.

Buses will be provided for transportation to the afternoon session at the Cleveland Clinic.

*Compliments of Wyeth Laboratories.

SECOND SESSION

THURSDAY AFTERNOON,
26 OCTOBER 1961

Attendance at the Postgraduate Course is limited to those who have registered and paid the matriculation fee.

This entire session will be held at the Frank E. Bunts Educational Institute of the Cleveland Clinic.

2:00 P.M.

Welcome–DR. CHARLES L. LEEDHAM, Cleveland, Ohio

2:05 P.M.

Review of Developments in Medicine, Cleveland Clinic
DR. A. CARLTON ERNSTENE, Cleveland, Ohio.

2:20 P.M.

6. **Hiatal Hernia, Medical Treatment.**
   DR. FRANCIS J. OWENS, Cleveland, Ohio.
7. **Hiatal Hernia, Surgical Treatment.**
   DR. DONALD B. EFFLER, Cleveland, Ohio.
8. **Colon Replacement of the Esophagus.**
   DR. RUPERT B. TURNBULL, JR., Cleveland, Ohio and DR. LAURENCE K. GROVES, Cleveland, Ohio.

3:00 P.M.

9. **Gastric Cytology.**
   DR. LAWRENCE J. MCCORMACK, Cleveland, Ohio.

3:15 P.M.

10. **Use of Cine Image Amplifier in Diagnosis of Upper Gastrointestinal Lesions.**
    DR. C. ROBERT HUGHES, Cleveland, Ohio.

3:35 P.M. Recess.

3:55 P.M.

11. **Cobalt 60 Therapy for Complicated Peptic Ulcer.**
Dr. Charles H. Brown, Cleveland, Ohio.

4:10 P.M.

12. **Indications for Surgery and Choice of Operation in Peptic Ulcer.**
Dr. Stanley O. Hoerr, Cleveland, Ohio.

4:30 P.M.

13. **New Developments in Cancer Research.**
Dr. George Crile, Jr., Cleveland, Ohio.

4:55 P.M.

Summation. Question and Answer Period.
Drs. Brown *(Moderator)*, Crile, Hoerr, McCormack and Owens.

5:20 P.M. Recess.

THIRD SESSION

THURSDAY EVENING,

26 OCTOBER 1961,

Attendance at the Postgraduate Course is limited to those who have registered and paid the matriculation fee.

Guests who have registered for the 26th Annual Convention of the American College of Gastroenterology, will be admitted to this session upon presentation of their badge.

This session and the following two sessions will again be held at the Sheraton-Cleveland Hotel.

7:30 P.M.

14. **The Fiberscope in Gastroscopy.**
Dr. Basil Hirshowitz, Birmingham, Ala. and Dr. William F. Fulton, Birmingham, Ala.

15. **The Flexible Scope and Biopsy in Gastroscopy.**
Dr. Harry Barowsky, New York, N. Y.

16. **Laparoscopy (Peritoneoscopy) with Endophotography and Guided Liver Biopsy.**
Dr. William S. Haubrich, Detroit, Mich. and Dr. Gustav A. Uhlich, Detroit, Mich.

9:00 P.M. Recess.

9:15 P.M.

17. **Biliary Tract Endoscopy.**
Dr. Clarence J. Schein, New York, N. Y. and Dr. Elliott S. Hurwitt, New York, N. Y.

18. **Diagnostic Proctosigmoidoscopy — Movie (22 minutes).**
Dr. Charles H. Brown, Cleveland, Ohio and Dr. Mauro Merlo, Cleveland, Ohio.

FOURTH SESSION

FRIDAY MORNING,

27 OCTOBER 1961

Attendance at the Postgraduate Course is limited to those who have registered and paid the matriculation fee.

9:00 A.M.

19. **Metabolic Changes and Management of Ascites.**
Dr. Harold P. Roth, Cleveland, Ohio.

20. **Metabolic Alterations Produced by Pyloric Obstruction.**
Dr. William D. Holden, Cleveland, Ohio.

21. **Management of Pyloric Obstruction.**
Dr. Harvey Dworkin, Cleveland, Ohio.

10:15 A.M. Recess.

10:45 A.M.

22. Causes and Management of Postgastrectomy Abnormalities.

Dr. William E. Abbott, Cleveland, Ohio.

11:15 A.M.

Question and Answer Period on Metabolic Changes.
Drs. Holden *(Moderator)*, Abbott, Dworkin and Roth.

a. From Question Box
b. Audience Participation

11:40 A.M.

23. Anemia in Gastrointestinal Disease.
Col. W. H. Crosby, Washington, D.C.

12:15 P.M.

Question and Answer Period
Audience Participation

12:25 P.M. Recess.

12:30 P.M.

LUNCHEON—Cleveland Room. For speakers and those taking the course.

FIFTH SESSION

FRIDAY AFTERNOON,
27 OCTOBER 1961

Attendance at the Postgraduate Course is limited to those who have registered and paid the matriculation fee.

2:00 P.M.

24. Panel Discussion on Gallbladder and Biliary Tract Diseases—Current Concepts in Diagnosis and Management.

Moderator
Dr. J. Edward Berk, Detroit, Mich.

Participants:
Dr. Robert J. Bolt, Ann Arbor, Mich.
Dr. Alfred M. Large, Detroit, Mich
Dr. Robert J. Priest, Detroit, Mich.
Dr. Herbert M. Stauffer, Philadelphia, Pa.

2:45 P.M.
Critique. Moderator and Participants.

3:35 P.M. Recess.

3:50 P.M.
Question and Answer Period. Moderator and Participants.

a. From Question Box
b. Audience Participation

5:00 P.M. Recess.

SIXTH SESSION

FRIDAY EVENING,
27 OCTOBER 1961

This session will be held in conjunction with the Cleveland Academy of Medicine at the Cleveland Academy of Medicine Building, 10525 Carnegie Avenue.

6:30 P.M.

Participants in this Postgraduate Course are invited to join the Cleveland Academy of Medicine at the Academy Building, for cocktails and dinner. Tickets are available at the Registration Desk of the Postgraduate Course in the Sheraton-Cleveland Hotel. It is requested that these tickets be obtained before noon, Friday, 27 October.

8:15 P.M.

Introduction: Dr. Henry Baker, Boston, Mass.

Academy Meeting.

25. Small Intestinal Malabsorption.

Dr. H. Marvin Pollard, Ann Arbor, Mich.

SEVENTH SESSION

SATURDAY MORNING,
28 OCTOBER 1961

Attendance at the Postgraduate Course is limited to those who have registered and paid the matriculation fee.

This session, and the afternoon session will again be held at the Sheraton-Cleveland Hotel.

9:00 A.M.

26. Neuropathways of Abdominal Pain.
Dr. Floyd M. Beman, Columbus, Ohio.

27. Bowel Complications of Surgery of the Abdominal Aorta.
Dr. William G. Pace, Columbus, Ohio.

28. Protein-losing Gastroenteropathies.
Dr. Daniel W. Elliott, Columbus, Ohio.

10:15 A.M. Recess.

10:45 A.M.

29. Scleroderma, Sarcoidosis, Collagen Diseases.
Dr. C. Joseph DeLor, Columbus, Ohio.

30. Gastrointestinal Parasites (Especially Amebiasis).
Dr. Donovan C. Browne, New Orleans, La.

12:00 Noon

Question and Answer Period on subjects of the morning.

Drs. Beman *(Moderator)*, Browne, DeLor, Elliott and Pace.

12:20 P.M. Recess.

EIGHTH SESSION

SATURDAY AFTERNOON,
28 OCTOBER 1961

Attendance at the Postgraduate Course is limited to those who have registered and paid the matriculation fee.

1:30 P.M.

31. Class. Methods in Cinegastrophotography.

Dr. Henry Colcher, New York, N. Y. and George M. Katz, New York, N. Y.

2:30 P.M.

32. X-ray Classroom.

a. Prepared questions. Collected by the Cleveland Chapter of the American College of Gastroenterology.

b. Answers with instructional demonstrations.

Director and Moderator:
Dr. Harry Hauser, Cleveland, Ohio.

Participants:
Dr. Eric vonBaeyer, Cleveland, Ohio.
Dr. Harry Gazelle, Cleveland, Ohio.
Dr. Norman Glazer, Akron, Ohio.
Dr. Mortimer Lubert, Cleveland, Ohio.
Dr. Robert O. Turek, Cleveland, Ohio.

Rebuttal:
Dr. Frank J. Borrelli, New York, N. Y.

c. Audience Participation if time allows.

4:30 P.M. End.

This Postgraduate Course, planned in cooperation with the Ohio State Academy of General Practice, is granted 17 hours of Category I credit for training, by the Ohio State Academy of General Practice.

SCIENTIFIC EXHIBITS

Booth A

Study of Successful Treatment of Peptic Ulcer

F. J. PHILLIPS, M.D., Quakertown, Pa.

Assuming that rest of both mind and stomach is essential therapy of peptic ulcer, a study was conducted to determine whether a tranquilizer-anticholinergic drug combination would provide these essentials in place of extra attention and reassurance from the physician. Fifty-nine private patients were divided into two groups. Each group was subjected to different physician-patient relationships. The first group was given brusk treatment with instructions on medication. The 29 patients in Group II, however, were given extra assurance and extra attention. From this work has evolved a successful methodology of symptomatic relief for peptic ulcer patients.

Booth B

Serial Observations in Healing of Peptic Ulcers and Physiologic Studies of Anticholinergic Therapy

LEONIDAS H. BERRY, M.D., F.A.C.G., Chicago, Ill.

This exhibit presents serial x-ray and gastroscopic views of various stages of healing of benign gastric ulcers. The locations of the lesions are on the lesser curvatures of the prepyloric antrum and in the body of the stomach. The smooth and progressive regeneration and replacement of the ulcerated areas by normal mucosa is demonstrated. These lesions are contrasted with the picture of so-called healing of a malignant ulcer. The lack of true epithelialization and smooth recession of the ulcer is brought out gastroscopically. There are charts and composite curves of gastric pH electrometrically determined before and after the oral and parenteral administration of an effective anticholinergic of low toxicity.

Booth C

A New Concept of the Etiology and Treatment of So-Called Functional Gastrointestinal Disease

JOSEPH BANDES, M.D., New York, N. Y.

A new concept of the etiology of "functional" gastrointestinal disease and its specific treatment is detailed. There is close association between active symptoms and demonstration in fecal smears of a spore-forming apparently never previousy described. The fungus diminishes in number and/or disappears as the patient improves with specific treatment.

Its occurrence is widespread and helps explain the poor results obtained in the past in many patients with peptic ulcer, angina (not due solely to coronary sclerosis), postcholecystectomy syndrome, "spastic colon", etc.

Photomicrographs of the fungus are presented and a simple staining procedure is demonstrated. The specific medication employed is explained and the clinical results obtained by its use in 200 patients are tabulated in detail.

Booth D

Ulcerative Colitis—A Hypersensitivity Disease

J. ALFRED RIDER, M.D., Ph.D., HUGO C. MOELLER, M.D., Ph.D., JOHN O. GIBBS, M.D. and JOYCE SWADER, B.S., San Francisco, Calif.

In this exhibit both clinical and experimental data is presented to show that some cases of ulcerative colitis may be attributed to hypersensitivity to food stuffs. A special 5-inch 24-gauge needle with an adjustable guard is used to inject the antigen into the rectal mucosa of these hypersensitive individuals. This needle is used through a proctoscope. Dilutions of wheat, milk and egg and a control are thus injected directly into the mucosa of the rectal wall. In those people who are sensitive to one or more of these food stuffs, there will be an immediate reddening and wheal formation in the area of injection. After the offending food stuff has been identified, the patient is treated by removing this food from the diet. The exhibit will present the excellent results obtained from this type of treatment.

As to the general pathogenesis of ulcerative colitis, this exhibit will show how, by various methods of sensitization, technically known as the Arthus, Shwartzman and Auer phenomenon, one can produce a picture much like ulcerative colitis in the bowel of rabbits. The microscopic characteristics in the sections from these animals are remarkably similar to that found from the areas of rectal mucosal testing in the human. Clinical and experimental findings will be correlated.

Booth E

Evaluation of a New Compound for Chronic Constipation

TIMOTHY A. LAMPHIER, M.D., F.A.C.G., Boston, Mass.

This study consists of a series of 91 patients. Patients were divided into age groups and are diagnosed as to the etiologic factor. A new compound has been evaluated as an aid in correcting this age old problem. The patient opinion of the drug action was used as a measure of patient acceptance as well as the result of the medical treatment by the medical investigator.

Booth F

Pancreatitis

WILLIAM G. PACE, M.D., RICHARD C. MCPHERSON, M.D. and GEORGE N. GRANT, M.D., Columbus, Ohio

This exhibit depicts the stages in the development of chronic pancreatitis, and the management of the disease at each stage of progression. On the left side of the exhibit, the factors involved in pancreatitis of biliary origin are presented, including the management of this type of pancreatitis. On the right half, the alcoholic etiology with treatment is presented. In the center of the back wall, there is a moulage of the pancreas with an outline for the management of chronic pancreatitis. Each phase of disease and its management is illustrated with color transparencies.

Booth G

Anticholinergics in Gastroenterology

F. STEIGMANN, M.D., F.A.C.G., Chicago, Ill.

The scope of this exhibit is to discuss the status of anticholinergic substances in clinical medicine and particularly in gastroenterology. By sketches and tables, the mode of action and the pathways of these actions will be shown. A discussion of the various types of anticholinergics as compared to atropine will be presented. By presentation of their chemical formulas, the differences between the natural anticholinergic and the synthetic substances will be demonstrated and the significance of these changes on their activity and side-effects discussed. Clinical observations on the effects and side-effects of several presently used anticholinergics will be discussed.

Booth H

Variations of Duodenal Diverticuli—Source of Unexplained Melena

MICHAEL M. KLEIN, M.D., ROBERT L. BRADLEY, M.D. and EMIL GRIBOVSKY, M.D., F.A.C.G., Huntington, W. Virginia

Duodenal diverticuli are far more frequent than are usually believed. There is a great variety in their size, location, appearance and number. In the past 10 years, 130 duodenal diverticuli were found in 4,000 gastrointestinal series. It is attempted to show the more interesting cases with special attention paid to those which were proven to be the cause of unexplained gastrointestinal bleeding.

Booth J

Gastric Tissue Changes in Association with Peptic Ulcer

EMMANUEL DEUTSCH, M.D. and HOWARD J. CHRISTIAN, M.D., Boston, Mass.

A ten-year study of gastric biopsies taken under gastroscopic observation has been carried out in more than 1,400 patients with indigestion. Safety of this procedure is demonstrated since no excessive bleeding or perforation occurred. The biopsy has regularly included a full thickness of gastric mucosa and its muscularis. Since it is impossible to target a small lesion, a minimum of 9 biopsies have been taken: 3 in the antrum, 3 in the body, and 3 in the fundus, in order to confirm the presence, frequency, type and extent of gastric pathology. During the past 3 years, general anesthesia for gastroscopy has facilitated the necessary follow-up of gastric tissue changes.

Study of a statistically significant group of biopsies has yielded a set of histological criteria for the definition of the normal and mild, moderate and severe chronic gastritis. Twelve per cent of our cases are normal. Eighty-two per cent are mild and moderate chronic gastritis representing *reversible* lesions which respond to medical management. Peptic ulcer of the stomach or duodenum in association with normal tissue, mild or moderate chronic gastric inflammation usually heals under medical management.

The severe form defines the intractable or *irreversible* lesion which occurs in six per cent of our cases. When the biopsy has exhibited severe

chronic gastric inflammation with simultaneous peptic ulcer, these patients have not responded to medical management and need immediate surgery.

Booth K

Nausea and Vomiting: Study of Phenothiazines, Thiethyperazine

DONOVAN BROWNE, M.D., F.A.C.G. (HON.), ROBERT D. SPARKS, M.D., PAUL GUTH, M.D., VICTOR FERRANS, M.D. and FRED HUNTER, M.D., New Orleans, La.

The neurophysiologic mechanism of vomiting is reviewed. The chemical structure and pharmacologic studies of a number of the phenothiazines are presented. The efferent pathways for vomiting are graphically demonstrated with a plastic brain model and electric circuits. Chemical localization and fluorescent studies of the operative vomiting are summarized. Experimental studies on gastric secretion, the effects of chronic administration, toxicity, radiation nausea, side-effects and other clinical applications are documented.

Booth L

Gastric Cytology

J. H. SMITH FOUSHEE, M.D., Z. A. KALNINS, M.D., ROBERT P. MOREHEAD, M.D., RAYMOND F. KAISER, M.D., FRITZ R. DIXON, M.D. and SIDNEY GIRSH, M.D., Winston-Salem, N. Carolina

Gastric cytology has been used by a number of investigators as an aid in the diagnosis of gastric cancer. The purpose of this study has been to find a simple, easy economical method for obtaining recognizable exfoliated gastric cells in sufficient numbers to establish a cytological diagnosis. A number of methods have been tried in order to achieve this aim. In-patients and out-patients were selected for this study who had gastrointestinal symptoms or signs.

This exhibit will demonstrate the correlation between gastric cytology and the pathology of the stomach in various diseases. The methods for doing gastric lavage are enumerated and the results obtained by these methods documented. Examples of various diseases of the stomach are illustrated by means of colorful photographs of cytological material and surgical specimens. Both benign and malignant diseases of the somach are discussed.

TECHNICAL EXHIBITORS

(Those attending the Convention sessions are urged to take advantage of the time in between the presentation of papers and sessions, to visit the technical exhibits and become acquainted with the many new products and new equipment on display.)

AIR-SHIELDS, INC., Hatboro, Pa. (Booth 29), will display the recently developed Kulich-Rousselot Tamponade Apparatus which provides a practical method to increase the effectiveness of balloon tamponade in emergency treatment of bleeding esophagogastric varices. A headgear unit controls traction on the gastric balloon and a manometer unit controls pressure in the esophageal balloon. An alarm, housed in a manometric unit, monitors both traction and pressure.

AMERICAN CYSTOSCOPE MAKERS, INC., Pelham Manor, N. Y. (Booth 25). The new fiber optic Gastroduodenoscope together with conventional operating and examining gastroscopes will be displayed. A cordial invitation is extended to visit their booth and representatives will welcome the opportunity to discuss these instruments.

AYERST LABORATORIES, New York, N. Y. (Booth 2), cordially invites you to visit their exhibit where *Riopan* and *Plegine* will be featured. Representatives will be pleased to discuss their products with you.

BORCHERDT COMPANY, Chicago, Ill. (Booth 21). *Maltsupex®* (Malt Soup Extract), liquid and powder. Laxative modifier of milk for constipated babies. Useful for geriatric constipation and pruritus ani. *Urolitia®*: for chronic urinary tract infections in older patients. Relieves burning urination. Especially useful for over a long period of time. *Ferromalt®* Tablets: nonconstipating Ferrous Sulfate Tablets. Good clinical response without usual side-effect of oral iron and are well tolerated.

BURTON, PARSONS & CO., Washington, D. C. (Booth 15). Their representative will be showing *Konsyl, L. A. Formula, neutraCarb,* and *EKG Sol.* Samples, descriptive literature and information will be available on all these products. *Konsyl* and *L. A. Formula* are the original refined psyllium bulk laxatives. *neutraCarb,* the antacid with Vitamin C has a delightful lemon flavor. *EKG Sol* is the new and modern electrode cream for electrocardiography and electroencephalography.

THE COCA-COLA COMPANY, Atlanta, Ga. (Special Area). Ice-cold Coca-Cola served through the courtesy and cooperation of The Cleveland Coca-Cola Bottling Co., and The Coca-Cola Company.

DOHO CHEMICAL CORPORATION, New York, N. Y. (Booth 13). *Dermoplast,* bactericidal and fungicidal aerosol spray especially useful in obstetrics and gynecology, following perineal suturing, etc. Also fast relief in surface pain, burns, wounds, abrasions, and sunburn. *Rectalgan,* liquid topical relief of pain and itching in hemorrhoids, pruritus, etc. Bactericidal and fungicidal. *Rectalyt HC,* revolutionized concept in proctologic medication and therapy. Water-miscible polymer vehicle containing Hydrocortisone-Sulfauridin. In a soft plastic, disposable, measured, uniform single dose, container-applicator.

EDER INSTRUMENT COMPANY INC., Chicago, Ill. (Booth 27), will again exhibit their latest devolpments in diagnostic instruments and call your special attention to—a gastric suction biopsy Sheath, a photographic Camera for Gastric photography and a teaching Telescope for the proctologist. All of these developments will be of great interest to the profession.

C. B. FLEET CO., INC., Lynchburg, Va. (Booth 1), will feature the *Fleet Enema* in the ready to use squeeze bottle. Attendants will be on hand to demonstrate how your rectal examinations can be made easier, faster and more revealing. Available also are literature and instructions on a safe, simplified and effective method of preparation for barium enema studies.

FLEMING & COMPANY, St. Louis, Mo. (Booth 8). *Marblen*—a new, and different antacid that is pink in color and has a peach-apricot flavor. *Marblen* is also sugar-free for the diabetic ulcer patient, and will not cause diarrhea or constipation. It will neutralize from 5-19 times as much acid as aluminum hydroxide preparations. You are invited to taste—try it.

E. FOUGERA & COMPANY, INC., Hicksville, N. Y. (Booth 22). Well-informed attendants will be on hand to make available product information and clinical literature on *Orabilex*—the advanced oral cholecystographic medium—and other products of interest to the gastroenterologist. You are invited to stop by.

GEIGY PHARMACEUTICALS, Yonkers, N. Y. (Booth 26), cordially invite you to visit their exhibit. They will feature important new therapeutic developments in the management of inflammation, as well as current concepts in the control of hypertension and edema; depression; obesity, and other disorders, which may be discussed with physicians and representatives in attendance.

GERIATRIC PHARMACEUTICAL CORP., Bellerose, N. Y. (Booth 5), pioneers in geriatric research, will exhibit *Gustase,* a triple enzyme containing a carbohydrate, protein and roughage digestant which works from the stomach through the colon; *Bilezyme,* a cholagogue and choleretic combined with starch and protein enzymes for the management of all liver and gallbladder disease associated with pancreatitis; *Gustalac,* the pleasant-tasting, fast and long-acting antacid.

GUARDIAN CHEMICAL CORP., L. I. City, N. Y. (Booth 24), will exhibit their *Clorpactin XCB* for destroying viable tumor cells in cancer surgery as well as their *Protractets,* which are a neutralizing and protective adjunct in the treatment of the peptic ulcer. They will also display their product, *Renacidin,* for preventing calcification of indwelling catheters.

LLOYD BROTHERS, INC., Cincinnati, Ohio (Booth 9), welcomes you to their exhibit. Their professionally trained sales representatives will be pleased to greet you and discuss the merits of their products in your practice.

McNEIL LABORATORIES, INC., Philadelphia, Pa. (Booth 17). Products to be featured at their exhibit are *Butisol Sodium®* butabarbital sodium, *Nacton®* poldine methylsulfate and *Nactisol*•.

•Trademark

PFIZER LABORATORIES, New York, N. Y. (Booth 12), invites you to visit their booth where their Professional Service Representatives will be pleased to discuss the latest topics of clinical interest.

PHARMACIA LABORATORIES, INC., Rochester, Minn. (Booth 6), will exhibit their *Azulfidine,* a new sulfa compound for the treatment of ulcerative colitis and regional enteritis. They will also display *Pharmalax,* the suppository with enema-like action. The action of *Pharmalax* causes defecation through mechanical stimulation of the intestinal musculature by carbon-dioxide released from the suppository. *Skopyl,* a new concept in the medical treatment of infant colic will also be shown. Literature and reprints will be available.

THE PURDUE FREDERICK COMPANY, New York, N. Y. (Booth 11) will feature *Senokot:* constipation corrective. Concentrated total senna glycosides which activate Auerbach's plexus, initiate normal neuroperistalsis. *Cardioquin:* a new polygalacturonate salt of quinidine. Indicated for cardiac arrhythmia.

REED & CARNRICK, Kenilworth, N. J. (Booth 18). *Phazyme,* the comprehensive approach to the treatment of gastrointestinal gas will be featured. In addition, new *Phazyme* with Phenobarbital will be introduced, offering all the advantages of *Phazyme* with the addition of Phenobarbital to allay the anxieties associated with aerophagia. *Modutrol,* total management of peptic ulcers as well as *Sycotrol,* the antianxiety drug indicated for gastrointestinal distress, will also be shown.

A. H. ROBINS COMPANY, INC., Richmond, Va. (Booth 7), will feature *Dimetapp Extentabs* and *Dimetane Expectorant. Dimetapp Extentabs* provides the unexcelled antihistaminic properties of *Dimetane* plus the decongestant actions of phenylephrine and phenylpropanolamine. With glyceryl guaiacolate these same compounds form *Dimetane Expectorant.* For expectorant action alone, prescribe *Robitussin,* and for a therapeutic multivitamin, *Adabee.*

ROCHE LABORATORIES, Nutley, N. J. (Booth 20), will exhibit *Librium,* a therapeutic agent for safe and fast control of nervousness, anxiety, tension and other common emotional disturbances without the dulling effect or depressant action of the tranquilizers. *Tigan,* a specific antiemetic agent effective both prophylactically and therapeutically against most clinically significant types of nausea and vomiting. Representatives will be pleased to discuss any questions you may have.

WILLIAM H. RORER, INC., Philadelphia, Pa. (Booth 16). *Maalox,* a pleasant tasting, nonconstipating antacid, is featured in Suspension, Tablets No. 1 and Tablets No. 2. Also highlighted are *Ascriptin;* a professional salicylate for pain of arthritis, *Chardonna;* an effective antispasmodic, *Parepectolin;* a pleasant tasting antidiarrheal preparation of paregoric, pectin and kaolin, and *Probutylin;* an oral anesthetic for the relief of nausea, vomiting, pylorospasm and gastritis. Representatives will gladly answer questions about their products.

SANDOZ PHARMACEUTICALS, Hanover, N. J. (Booth 10). As a sequel to the original research which led to the synthesis of *Mellaril*, a tranquilizer relatively devoid of antiemetic activity, they have now developed a potent antiemetic, with little or no tranquilizing properties. This compound, *Torecan*, constitutes a specific antiemetic and the results indicate that it is a promising agent for the treatment of nausea and emesis of diverse etiology. Representatives will answer questions about their products.

E. R. SQUIBB & SONS, New York, N. Y. (Booth 28), has long been a leader in development of new therapeutic agents for prevention and treatment of disease. The results of their diligent research are available to the Medical Profession in new products or improvements in products already marketed. They will be pleased to present up-to-date information on these advances for your consideration.

WALLACE LABORATORIES, Cranbury, N. J. (Booth 23). Their representatives will be glad to discuss *Milpath* (*Miltown* plus anticholinergic) which relieves anxiety and tension for enhanced control of pain, spasm, hypermotility and hypersecretion in ulcer and other gastrointestinal disorders. A new potency, *Milpath* 200, has been made available. It contains only half the *Miltown* but the same amount of tridihexethyl chloride as *Milpath* 400.

WINTHROP LABORATORIES, New York, N. Y. ris Plains, N. J. (Booth 19), will feature, *Gelusil*—the physician's antacid—for the relief of gastric hyperacidity and management of peptic ulcer. Provides two protective coating gels for prompt, prolonged relief of pain. *Gelusil* is all antacid in action—is non-constipating, contains no laxative.

THE WARREN-TEED PRODUCTS CO., Columbus, Ohio (Booth 31), will feature *Ilopan®* —Choline Tablets: oral therapy for the treatment of gastrointestinal gas retention in ambulatory patients. *Ilopan®*: an injectable d-pantothenyl alcohol for the treatment and prevention of flatulent gastrointestinal distention. *Modane:* a laxative for rehabilitation and relief of the antonic bowel, and *Kaon®*—an extremely palatable oral potassium. Representatives will cordially welcome you to their display.

WINTHROP LABORATORIES, New York, (Booth 30), will feature *Alvodine*, a new potent narcotic analgesic that relieves pain without causing drowsiness or hypnosis (in over 90 per cent of patients). It is well suited for postoperative use, for pain from cancer, angina, cholecystitis, pleurisy, myocardial infarction; also for preoperative preparation and as a supplement to anesthesia. *Alvodine* is highly effective orally as well as parenterally. It is available in scored tablets of 50 mg. and ampuls of 20 mg. (1 c.c.), subject to Federal Narcotic Law.

WYETH LABORATORIES, Philadelphia, Pa. (Booth 14), will feature *Oxaine® M* (Oxethazaine in alumina gel with magnesium hydroxide, Wyeth) providing sustained mucosal anesthesia to relieve pain and discomfort in esophagitis, gastritis, peptic ulcer, and irritable bowel syndrome. Also featured will be *Polymagma®* and *Diamagma®* for bacterial and nonbacterial diarrheas. Both products contain the superior adsorbent *Claysorb®* (Activated attapulgite, Wyeth).

ABSTRACTS FOR GASTROENTEROLOGISTS

GASTROINTESTINAL TRACT

PERFUSION TREATMENT OF PATIENTS WITH CANCER: O. J. Creech, Jr., E. T. Krementz, R. F. Ryan, Keith Reemtsma, J. L. Elliot and J. N. Winblad. J.A.M.A. 171:2069 (12 Dec.), 1959.

Perfusion technics in the treatment of patients with cancer consist in circulating solutions of anticancer drugs through the blood vessels. The authors found no specificity of an agent for a given tumor. The object of the method is to increase the concentration of the drug and at times to confine it as much as possible to the area being perfused. In the case of a limb the artery and vein, and an extracorporeal circuit are used; in case of the lungs two circuits; in generalized carcinomatosis total-body perfusion is used; bone marrow from the sternum and iliac crests is first removed to protect it from the drug and then the marrow is reinjected. The authors treated 145 patients with 8 operative deaths. There were no cures; the complications in most instances were not serious. The treatment was most effective for malignant melanoma.

SAMUEL L. IMMERMAN

ESOPHAGUS

TREATMENT OF BLEEDING ESOPHAGEAL VARICES: M. J. Mackby. J.A.M.A. 171:1916 (5 Dec.), 1959.

Massive upper gastrointestinal bleeding is due to peptic ulcer in about two out of three cases. About one-third of these hemorrhages are due to bleeding esophageal varices. The author advocates the emergency use of the Sengstaken tube for diagnosis and treatment as the first measure. He uses the tube for 24-48 hours. During the period the balloon is inflated 1 gm. of neomycin is administered every four hours and purgatives (2 oz. of magnesium sulfate) are given through the tube; these preparations and colonic irrigations are given in an attempt to flush out the blood in the intestinal tract. If there is any sign of impending coma or ammonia intoxication, 40 gm. of arginine in 400 c.c. of dextrose is administered; this treatment is repeated two to four times in 24 hours. Blood loss is replaced fully. If bleeding recurs after the balloon is deflated, the patient is taken to surgery and, usually through an abdominal approach, the varices are ligated. The abdominal approach allows the surgeon to rule out a peptic ulcer as the cause of the hemorrhage. Some patients have been known to rebleed from esophageal varices within six weeks after surgical ligation.

Therefore, it is desirable to retain such patients in the hospital for a period of 3-6 weeks after emergency ligation of varices and to prepare them for definitive shunt construction as soon as their condition will warrant such a procedure. The end-to-side portacaval shunt is preferred, and is recommended for all patients who have had recurrent bleeding from proved esophageal varices, who are not jaundiced, and who show no signs of ammonia intoxication. Such patients should be brought to the optimum level of hepatic function prior to surgery. Splenorenal shunt is recommended for all those patients with extrahepatic block who have a splenic vein over 1 cm. in diameter.

SAMUEL M. GILBERT

THE COLON AS REPLACEMENT FOR THE ESOPHAGUS: ITS RESISTANCE TO REFLUX OF GASTRIC JUICE: Joseph J. Schechter, Jose J. Yap and Richard H. Segnitz. Wisconsin M. J. 58:677 (Dec.), 1959.

This is a study on dogs to determine how a substituted segment from the right colon would tolerate reflux of gastric juice and how it would function as a passageway over a period of time.

One dog was sacrificed at the end of four weeks; seven dogs were observed over a period of approximately a year. Histamine stimulation induced ulceration. Vagotomy appeared to protect these dogs. The conclusions were that the colon functions well as a passageway and is vulnerable to gastric juice under conditions of hypersecretion.

BERNARD FARFEL

FAMILIAL ESOPHAGEAL EPIPHRENAL DIVERTICULA: W. E. Hird and C. B. Hortenstine. J.A.M.A. 171:1924 (5 Dec.), 1959.

Demonstration of multiple epiphrenal diverticula in a male parent and two of his children, with tracheoesophageal fistula found at birth in a grandchild, lends strong support to the concept that familial genetic defect is a possible etiological factor. The diverticula in these reported cases were found to extend over the entire lower esophageal segment. The male parent had no symptoms until the age of 40, then developed only moderately pronounced symptoms over a period of 30 years and without development of any severe complications. Therefore conservative therapy is advised in these cases since extensive resection would be necessary to remove the entire involved segments.

SAMUEL M. GILBERT

PEPTIC ESOPHAGITIS COMPLICATED BY ESOPHAGEAL ULCER AND OBSTRUCTION: Thomas C. Case. J. Internat. Coll. Surgeons 32:613 (Dec.), 1959.

The surgical procedure employed in this instance merits attention. It conserves considerable physiologic components that aid in securing good digestion and ample nutrition.

It is a very interesting case report. A full study of the article is recommended.

IRVIN DEUTSCH

STOMACH

RECOVERY FOLLOWING PERFORATED PEPTIC ULCER: R. D. Weir and C. U. Webster. Scottish M. J. 4:481 (Oct.), 1959.

Ninety-eight per cent of all perforated peptic ulcer patients survived the operation and a 6-month postoperative period in the Aberdeen Royal University Infirmary.

Eight weeks was the average convalescence period before returning to work. It is believed that in the absence of an organized rehabilitation program eight weeks is probably a minimum convalescence.

A longer convalescence appeared to be desired by most patients but economic considerations and the type of work were influencing factors.

A. M. SUSINNO

SIMULTANEOUS GASTRIC DUODENAL ULCERS IN A 15-YEAR OLD BOY. (CASE REPORT): Cornelius Colangelo. Illinois M. J. 116:214 (Oct.), 1959.

The authors state that gastric and duodenal ulcers coexist in one per cent of ulcer cases. In their case this happened in a 15-year old boy which is even more unusual. They also state that the symptomatology of ulcer is often minimal or even absent. Gastric ulcer may appear and disappear rapidly and the authors state their belief that gastric ulcer of the vertical part of the stomach is different from that of the antrum and duodenal cap. This was the case in their patient, who had few symptoms and recovered rapidly on medical treatment.

SAMUEL L. IMMERMAN

DUODENAL ULCER: SOME OBSERVATIONS ON PATHOGENESIS: C. Joseph DeLor and Floyd Beman. Ohio M. J. 55:1376 (Oct.), 1959.

Increased gastric secretion with marked increases in hydrochloric acid pepsinogen levels have repeatedly been found in duodenal ulcer. All foods stimulate gastric secretion. However, some, such as coffee, tea, seasonings, and alcohol, produce more profound sustained levels of hypersecretion. Many commonly prescribed drugs, such as salicylates, caffeine, phenylbutazone, are ulcerogenic. The hormones have an equivocal effect on gastric juice, but appear to have an adverse effect in the presence of ulcer. Psyche and heredity play a role in the pathogenesis of this disease, as well as burns and intracranial lesions.

While the specific etiology is unknown, duodenal ulcer is more comon in people with Type O blood. There is no clear cut evidence to support the existence of an ulcer personality. Some individuals are supersecretors. Stress, emotional storm, burns, intracranial lesions, and drugs may precipitate an ulcer in the presence of this hypersecretory state.

SAMUEL M. GILBERT

SURGERY FOR CHRONIC DUODENAL ULCER: COMPARISON OF RESULTS WITH VAGOTOMY-POSTERIOR GASTROJEJUNOSTOMY AND WITH VAGOTOMY-HEMIGASTRECTOMY; EVALUATION OF A PERSONAL SERIES OF 200 PATIENTS: Stanley O. Hoerr. Cleveland Clin. Quart. 26:170 (Oct.), 1959.

This is an evaluation of certain surgical procedures carried out by the author in 200 cases. The procedures were vagotomy-gastrojejunostomy and vagotomy-hemigastrectomy. For duodenal ulcer vagotomy-hemigastrectomy is considered to be much more effective against recurrent ulceration than vagotomy-gastrojejunostomy, but the latter procedure is considered safer in poor risk patients. A list of the criteria used to determine success or failure of the procedures is enclosed and discussed.

IRVIN DEUTSCH

THE PROXIMAL LIMIT FOR SUBTOTAL GASTRIC RESECTION: Arnold L. Lehmann. Northwest Med. 58:1559 (Nov.), 1959.

The author stresses the importance of knowing the proximal limit of gastric resection in the pursuit of more extensive removal of the stomach for treatment of carcinoma or gastric or duodenal ulcer. The author presents a case study in which a small segment of the stomach was preserved. The problem of resecting a large gastric tumor without removing all of the stomach was met by leaving a small portion of the stomach. It was followed by gratifying palliation. If the blood supply to the stomach is reduced severely then a small gastric remnant is more likely to escape ischemic necrosis. The diaphragmatic cuff should be carefully preserved. Keeping in mind the anatomy of the proximal segment of the stomach, it has been possible to extend the limit of gastric resection.

BERNARD J. FICARRA

INTESTINES

NEWER DEVELOPMENTS IN PROCTOLOGY: Donald C. Collins. Am. J. Proct. 10:283 (Aug.), 1959.

Phenylbutazone is used to speed convalescence in acutely thrombosed hemorrhoids. While the drug possesses no lytic properties, its anti-inflammatory and analgesic effects intracellularly reduces edema and perivascular infiltration.

Six hundred mg. is given orally for three days, then a maintenance dose of 300 mg. is continued for six days. Nine-day use of the drug precludes specific toxicity of the preparation.

A liver polypeptid (Feramid), molecular weight 11,000 which detoxifies guanadine, has been used experimentally upon patients for the relief of arthritis, but it was noted that the drug relieved pruritus ani and anorectal inflammations.

Five c.c. administered intramuscularly two or three times a week until desired results are obtained, usually bring permanent relief.

J. Edward Brown

APPENDICEAL-VESICAL FISTULA: Samuel Hyman and N. J. Capos. J.A.M.A. 170:2177 (29 Aug.), 1959.

Although acute perforative appendicitis with the formation of an appendiceal-vesical fistula is quite a rare condition the authors were able to discover three such patients within a short period of time. The causative lesion is an acute pelvic appendicitis with adhesion of the distal end of the appendix to the bladder wall, abscess formation, and rupture into the bladder. The three cases reported were all males since the interposition of the uterus and female adnexa between the bladder and intestine prevents this complication in women.

The symptoms of appendiceal-vesical fistula are variable and may include 1. gastrointestinal complaints which are consistent with acute pelvic appendicitis in early stages and vague abdominal pain and diarrhea in late stages, 2. urinary symptoms which vary from those of a mild infection to those of a marked cystitis with feces and gas in urine, and 3. chronicity, measured in months or years, because the condition is not recognized.

The diagnostic possibility of appendiceal-vesical fistula should be kept in mind when patients have a history of gastrointestinal and urinary complaints combined with the passage of gas and feces in the urine.

Louis A. Rosenblum

NEW TREATMENT FOR ULCERATIVE COLITIS: L. W. Granirer. J.A.M.A. 171:402 (26 Sept.), 1959.

The author reports a case of fulminating ulcerative colitis in a 32-year old woman, with a rapid pulse, elevated temperature, low blood pressure, and 10-14 stools daily. Blood, saline, steroids and antibiotics were administered without improvement. Then ACTH and 5 mg. of gold were given intravenously and 50 mcg. of Vitamin B_{12} subcutaneously. Next day she showed a dramatic improvement, with a drop in temperature and pulse rate, and reduction in the number of stools. Phenylbutazone 100 mg. was given daily. The ACTH was given for 21 days in a total dose of 140 units, which is considerably less than that usually employed. The patient was maintained on gold and Vitamin B_{12} twice weekly without any dietary restriction whatever.

The author believes that the gold, Vitamin B_{12} and phenylbutazone corrected the disease process. It seems likely, however, that the ACTH played a decisive role in the sudden improvement manifested by the patient, especially since such dramatic improvement has been reported by others following corticotropic hormone.

Arnold Stanton

TREATMENT OF TAPEWORM INFECTIONS IN MAN: W. H. Jopling and A. W. Woodruff. Brit. M. J. 5151:542 (26 Sept.), 1959.

The authors present information on the treatment of tapeworm infections under standard conditions in 240 cases.

No statistically significant difference in

results was found between five different treatment regimes, including administration of male fern orally or by duodenal tube and of mepacrine by the same routes.

Factors which may give rise to poor results when these regimes are used include inadequate fasting, administration of male fern in capsules instead of in a liquid, and, when doses of anthelmintics of small volume are administered through a duodenal tube, failure to take into account the amount required to fill the tube before any is delivered from its distal extremity.

Unfavorable false impressions of the efficacy of a treatment for tapeworm may be obtained unless patients are followed up for at least four months in cases in which the head of the worm is not recovered after treatment. Failure of treatment due to vomiting was encountered more often among those treated with mepacrine than with male fern. As vomiting in patients with *T. solium* infections may give rise to cysticercosis, treatment with mepacrine in such cases is best avoided.

LOUIS A. ROSENBLUM

MASSIVE RESECTION FOR ILEITIS: Mandel Weinstein, Morton Roberts and Brian Reynolds. J.A.M.A. 171:396 (26 Sept.), 1959.

The authors report two cases of extensive resection for ileitis 12 years after operation. The first patient was 47 years old at the time of operation and was left with only the duodenum and two feet of jejunum and portions of colon. The second patient was 20 years old and was left with the duodenum, 1½ feet of jejunum, descending colon and part of the transverse colon.

After operation there is compensatory hypertrophy of the remaining portions of intestine, and these patients improve greatly with time. In the beginning there is impaired absorption of protein and fat, but later these are absorbed as readily as carbohydrates. Water absorption remains unchanged leading to diarrhea which is regulated effectively by the patients themselves.

ARNOLD STANTON

SO-CALLED PRIMARY ULCEROHYPERTROPHIC ILEOCECAL TUBERCULOSIS: F. F. Paustian and H. L. Bockus. Am. J. Med. 26:509 (Sept.), 1959.

A case of ulcerohypertrophic ileocecal tuberculosis, in the absence of pulmonary disease is reported. An excellent result following surgical resection and subsequent antitubercular therapy.

JOHN M. MCMAHON

LIVER AND BILIARY TRACT

A COMPARISON OF THE CEPHALIN-CHOLESTEROL FLOCCULATION AND THYMOL TURBIDITY TESTS IN PATIENTS WITH PORTAL CIRRHOSIS: O. K. Litherland and A. Bogoch. Canad. Med. Ass. J. 80:958 (15 June), 1959.

The cephalin-cholesterol flocculation and thymol turbidity tests reflect derangements in the serum proteins.

It would appear that if the upper limit of the cephalin-cholesterol flocculation test is taken as either plus 1 or plus 2, and the upper limit of thymol turbidity as 4.6 units, the thymol turbidity test is more likely to be abnormal. The same is true when the upper limit of cephalin-cholesterol flocculation is taken as plus 2 and the thymol turbidity as 8 units. The cephalin-cholesterol flocculation test more often gives abnormal results when its upper limit is taken as plus 1 and the upper limit of thymol turbidity is taken as 8 units.

There was no evident correlation between the levels of these two tests, except that the highest levels of thymol turbidity occurred when cephalin-cholesterol flocculation was most abnormal (4 plus).

There is a linear correlation between the average thymol turbidity and cephalin-cholesterol flocculation levels up to and including plus 3 flocculation. Insufficient data were available to compare the tests when the cephalin-cholesterol flocculation was plus 4.

Forty-eight and 50 per cent of patients had normal cephalin-cholesterol flocculation and thymol turbidity tests respectively on one or more occasions. It is considered that neither of these nonspecific tests is to be preferred. In the assessment of the patient with cirrhosis, it may be advantageous to perform both of them.

No relationship could be demonstrated between the levels of serum bilirubin and values of thymol turbidity or cephalin-cholesterol flocculation.

I. HENRY EINSEL

CHANGES IN COLLOID OSMOTIC PRESSURE OF THE BILE IN CASES WITH BILIARY DISEASE: I. EXPERIMENTAL STUDIES ON THE GALLBLADDER BILE OF DOGS: Makoto Maruyama. Tohoku J. Exp. Med. 70:11 (25 June), 1959.

Experiments were conducted on 20 dogs after 12 hours of fasting. The gallbladder was punctured and the colloid osmotic pressures of the bile were obtained. The biliary dyskinesia was then produced by dilating the muscle of Oddi by inserting a Nélaton's catheter No. 3 transduodenally in the papilla of Vater for a specified time.

They recorded the pressures of the gallbladder before dyskinesia was performed and then 4 to 35 days later. The normal values were 627 and 646 mm. H_2O. After dyskinesia was performed the values were 739 and 752 mm. H_2O, showing an increase of 112 and 106 mm. H_2O. This was an increase of 18 and 16.5 per cent.

The above experimental work was performed because of clinical invasion of the biliary tree by ascaris. The parasites having membrane act as a semipermeable membrane. Through this membrane, the body fluid of ascaris is forced to come in contact with the bile whose colloid osmotic pressure is much higher than that of the former. The parasitic invasion of the biliary tract gives rise to a considerable disturbance of the papilla of Vater which causes the secondary dyskinesia, resulting in further increase of colloid osmotic pressure of the first.

The experimental data explains why the body of the ascaris in the biliary tract is subjected to a severe dehydration due to the difference in the colloidal pressure and why it is putrefied and flatted and hardened in a few days.

I. HENRY EINSEL

CHANGES IN COLLOID OSMOTIC PRESSURE OF THE BILE IN CASES WITH BILIARY DISEASES. II. CLINICAL OBSERVATIONS: Makoto Maruyama. Tohoku J. Exp. Med. 70:17 (25 June), 1959.

This paper is a continuation of the experimental work of the author in a previous paper (Part I).

The experiments were performed on 25 cases, consisting of 9 cases of noncalculous cholecystitis, 10 cases of cholelithiasis, 2 cases of biliary tract ascariasis, and 4 cases used to control.

At the time of surgery the bile was collected by a puncture of the gallbladder. The colloid osmotic pressure was measured by Kroh-Nakazawa's first method.

The conclusions were as follows: The colloid osmotic pressure was generally higher than in the control. The pressure was the highest in the biliary tract ascariasis, and higher in noncalculous cholecystitis and in cholelithiasis, in the order mentioned.

The colloid osmotic pressure of the pathological bile was 3 to 4 times as high as that of the body fluid of ascaris. This is the probable reason why a dead body of ascaris is able to remain in the biliary tract for a long time without suffering putrefaction.

These observations and findings would be important where the incidence of ascaris infection is high.

I. HENRY EINSEL

BLOOD DISAPPEARANCE OF RADIOACTIVE ROSE BENGAL—RAPID SIMPLE TEST OF LIVER FUNCTION: R. A. Nordyke and W. H. Blahd. J.A.M.A. 170:1159 (4 July), 1959.

A technic of administration of I^{131}-labeled rose bengal for determination of liver function is described. Readings taken on the lateral aspect of the head were felt

to represent the input to the liver. External counting over the abdomen, below the liver were taken to represent the output of dye from the biliary tract to the intestine. This paper describes the changes mainly occurring in liver disease in the input phase, which is thought to determine the rate of disappearance of dye from the blood. This is correlated with other tests and has obvious advantage in the presence of jaundice. In borderline liver dysfunction, it is felt to be a more sensitive test than the bromsulfalein test.

BERNARD FARFEL

GAS-CONTAINING GALLSTONES: L. K. Mark. J.A.M.A. 170:1531 (25 July), 1959.

Gas-containing gallstones may, by their characteristic stellate radiolucency, be the only evidence of gallbladder disease. Although less than 30 cases have been reported, it is believed that they have a greater frequency rate.

Gas within gallstones is found only in mixed, radially constructed, fissured gallstones. Fissuring occurs due to shrinkage of the stone as a natural aging process, with the consequent development of a central void and negative pressure which encourages the diffusion of either gas or fluid from adjacent tissues, depending upon the physical qualities of the calculus.

These stones are easily identifiable radiographically on the routine P.A. and oblique projections of the abdomen.

EZRA J. EPSTEIN

HEPATIC COMA: Mahlon Delp, Robert Manning and Robert Brown. Mississippi V. Med. J. 81:189 (July), 1959.

Hepatocerebral intoxication (HCI) is a more appropriate term to use than hepatic coma, because not all patients so afflicted develop true coma. HCI may be defined as a clinical syndrome in which central nervous system signs and symptoms may range from mild mental and neurological defects to severe, progressive irreversible changes and death.

The role of ammonia intoxication whether due to excessive accumulation or the inability to metabolize normal concentrations, has not as yet been firmly established. There may be other offending substances present.

Three clinical variants of the HCI symptom-complex have been recognized: 1. Precoma; 2. Episodic HCI; 3. Coma.

In the first group with any kind of liver disease, the early signs of cerebral involvement as irritability, confusion, agitation, lethargy, weakness, may all be present but can easily be reversed or spontaneously subside with complete recovery.

The second group is almost entirely confined to the cirrhotics with extensive collateral circulation, and is usually induced by those factors which produce an elevated blood ammonia level, and is corrected by eliminating these ammoniagenic factors. This group represents the most favorable prognostically speaking.

Management of these patients is facilitated by establishing three prognostic categories, to wit:

1. Progressive symptoms for less than 24 hours with the ammoniagenic factors easily controlled.

2. Progressive symptoms for more than 24 hours with the ammoniagenic factors controlled with difficulty.

3. Nonremedial underlying disease (neoplesia, massive necrosis, etc.) with the ammoniagenic factors uncontrollable.

EZRA J. EPSTEIN

BIOPSY OF THE LIVER WITH THE VIM-SILVERMAN NEEDLES: Charles H. Brown. Mississippi V. Med. J. 81:198 (July), 1959.

Biopsy of the liver with the Vim-Silverman needle has greatly added to our knowledge of liver disease, and especially that of infectious and serum hepatitis. Our prior information about these diseases was obtained only from postmortem studies which gave only partial knowledge of the pathology as most cases recovered from the acute episodes.

Two methods of approach have been ad-

vocated for varying circumstances. The subcostal approach is recommended where liver enlargement exists, and the thoracic or intracostal aproach is suggested where there is no palpable liver because of the probable tamponade effect of the diaphragm. The technic is described in detail.

The indications for needle biopsy are:

1. Unexplained hepatomegaly;
2. Hepatic dysfunction;
3. Suspected malignancy—primary or secondary;
4. Suspected granuloma of liver;
5. Jaundice not clearly defined by the usual clinical and laboratory studies.

The contraindications have been listed as:

1. Prothrombin time less than 75 per cent;
2. Decrease platelet count or other bleeding tendencies;
3. Infection as liver abscess or peritonitis;
4. Uncooperative patient;
5. Presence of ascites;
6. No definite indication for biopsy.

There has been a minimum of complications in over 800 cases.

EZRA J. EPSTEIN

PANCREAS

THE CHOICE OF SURGICAL PROCEDURES IN THE TREATMENT OF PANCREATITIS: F. M. Simmons Patterson. North Carolina M. J. 21:1 (Jan.), 1960.

Based on physiologic facts, the following operations have been advocated in an effort to reduce the output of pancreatic juices: vagotomy, vagotomy plus gastroenterostomy, vagotomy plus subtotal gastrectomy, and subtotal gastrectomy alone. In addition to the above procedures direct operations on the pancreas have been employed such as: pancreatolithotomy, transduodenal exploration and dilatation of the pancreatic ducts, retrograde surgical drainage of the pancreas, pancreaticojejunostomy, pancreaticogastrostomy, anastomosis of the duct of Wirsung to the gastrointestinal tract, ligation of the pancreatic ducts, distal pancreatectomy, total and partial pancreatectomy.

The authors conclude that it is of the utmost importance that appropriate surgical treatment of chronic pancreatitis be instituted before there is marked destruction of the pancreas (parenchyma). The many variations and pathologic findings encountered in patients with this complex condition make it absolutely necessary that surgeons be familiar with the various procedures in order to select the appropriate one for the individual patient. No single operation will be applicable to every case. If doubt exists at the operating table as to the main pathologic condition to be corrected, it would seem wise to employ a conservative operation first. Often this will be successful. If it should fail, a more radical procedure can be performed later. If the etiologic factor in the individual case can be accurately determined, the choice of operation will be greatly simplified.

BERNARD J. FICARRA

PATHOLOGY AND LABORATORY RESEARCH

BLOOD GROUPS OF GASTRIC ULCER AND CARCINOMA: W. H. Beasley. Brit. M. J. 5180:1167 (16 Apr.), 1960.

Various investigators have had different results attempting to correlate blood groups and gastric cancer and ulcer. Some have denied any difference between persons with various blood groups. However, in recent years the majority found that group A prevailed in cancer of the stomach. Therefore, 780 patients were investigated by the author who found a relationship between group A and gastric cancer and at the same time a prevalence of group O and gastric ulcer in an additional similar group of persons. He reached the conclusion that genetic factors play some role, but probably not the major role, in the development of these diseases.

H. B. EISENSTADT

UROPEPSINOGEN LEVEL IN POSTGASTRECTOMY CASES: J. Malcolm Cameron. Brit. M. J. 5180:1182 (16 Apr.), 1960.

Uropepsinogen excretion reflects quantitatively the gastric pepsin output. It does not disturb the patients and avoids artificial stimuli that may influence the results of laboratory tests. Therefore, uropepsinogen output was determined in 75 postgastrectomy patients. The level varied between 0 and 5.8 units per hour. Persons with good surgical results had a level of less than 3.0 U.P./hr. Those with poor results had more than 5 units. Therefore, uropepsin excretion can be used as a good measurement to estimate the succes of gastrectomy provided, however, that the 24-hour urine collection is accurate.

H. B. EISENSTADT

SIMPLE TUBELESS GASTRIC ANALYSIS BY THE DESMOID PILL TECHNIC: Richard D. Levere and Eddy D. Palmer. U. S. Armed Forces M. J. 11:781 (July), 1960.

In Europe, a preparation for tubeless gastric analysis that eliminates the need for chemical determinations has been extensively used with popularity. Known as the "desmoid pill" (Desmoidpillen, Pohl), the preparation was devised by Sahli in 1905. The pill consists of a small, hard ball of methylene blue wrapped in a thin rubber sheet which is tied with plain catgut. Two turns of the catgut are made around the gathered edge and the ends are then tucked under the resulting loops, pulled tight, and cut short.

In the presence of normal gastric secretions the knot opens, with release of methylene blue, which is absorbed and then excreted in urine, to which it imparts a diagnostically blue or blue-green color. In event of achlorhydria, the pill passes undisturbed through the gastrointestinal tract with no absorption of the dye. The pill is administered one-half hour after intake of a cup of black coffee on a fasting stomach. The urine was then closely observed for any color change during the next 24 hours.

The preparation was administered to 42 patients whose gastric juice contained free HCl and to 9 patients with achlorhydria by gastric analysis. A check of the results, using the usual stomach tube and histamine stimulation, revealed a sufficient correlation of results to indicate that the test is a fairly reliable method of screening patients for achlorhydria, requiring nothing more than a desmoid pill and a cup of coffee.

JOSEPH E. WALTHER

THE RELIABILITY OF THE SERUM AMYLASE DETERMINATION: T. F. Boyd, M. B. Boyd and J. J. Byrne. Am. J. Digest. Dis. 5:499-522 (June), 1960.

The level of serum amylase activity may be influenced by many disease processes reported in the past. The authors studied the less known physical and physicochemical changes affecting amylase activity and attributable to methods of handling or storing the blood specimen. It is suggested that the serum be separated from the blood cells and stored at 8° C. if the determination can't be done right after withdrawal of the specimen. Glassware used for the test should be repeatedly rinsed with distilled water to avoid errors caused by the most minute residue of a cleansing agent. Another potential source of error is a partly hemolytic specimen. No effects on the level of serum amylase activity were found from the serum contents of chloride, calcium, alcohol, bilirubin, and urea.

WALTER CANE

A SIMPLE, RAPID SCREENING TEST FOR SERUM AMYLASE: Adrian Hainline, Jr. and Stanley O. Hoerr. Am. J. Surg. 100:5 (July), 1960.

A high value for serum amylase is widely regarded as the single most important laboratory finding to help establish a diagnosis of acute pancreatitis. This method of determining the serum amylase can be completed within 20 minutes, requires a mini-

mum of equipment, and is easily taught to interns, residents, and night laboratory personnel. The authors present the steps in detail.

A case report is submitted of the value of the rapid screening test for serum amylase and this was subsequently corroborated by standard methods of determination.

CARL J. DEPRIZIO

PSYCHOSOMATIC MEDICINE

FUNCTIONAL DISTURBANCES OF THE SMALL AND LARGE BOWEL: Jeptha R. MacFarlane. Am. J. Proct. 10:352 (Oct.), 1959.

The writer reviews the essentials of the psychodynamic organization of bowel functions. He briefly describes various functional disorders such as chronic appendicitis, regional enteritis, ulcerative colitis, and small intestinal spasm.

The psychodynamics of constipation and enteroptosis are discussed in some detail.

THEODORE COHEN

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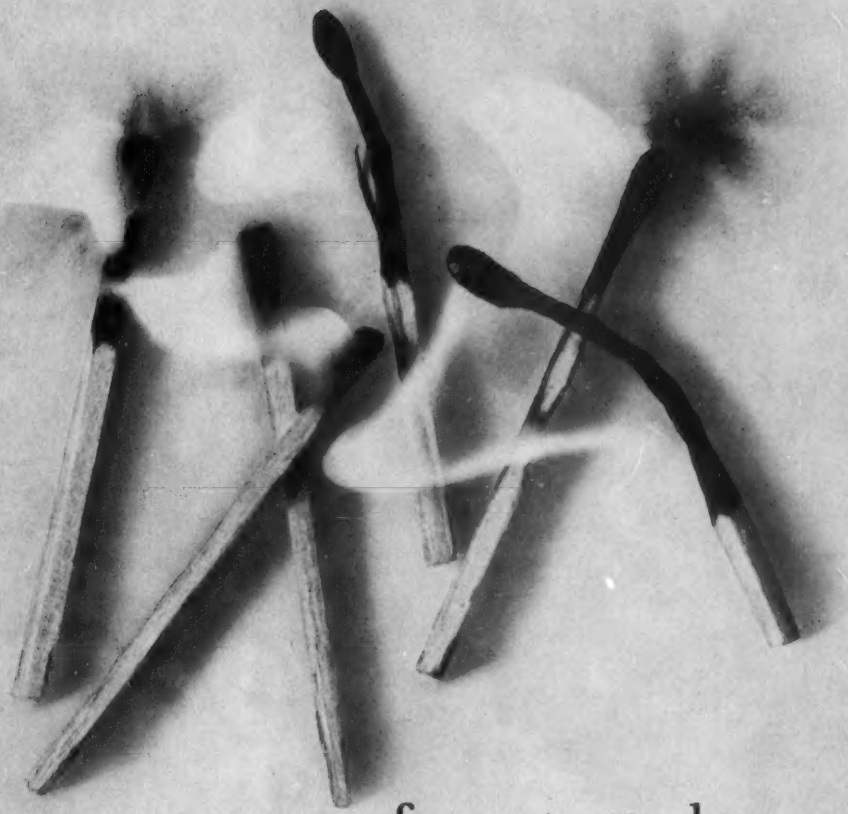

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℞ ENARAX®

(oxyphencyclimine plus ATARAX®)

In peptic ulcer and functional bowel distress
ENARAX provides dual relief of symptoms: it decreases acid flow and spasm...and relieves tension.

Plus protection against flare-ups
ENARAX works continuously...gives dependable 24-hour control, usually with b.i.d. dosage.

Here's how: ENARAX combines oxyphencyclimine, an inherently long-acting anticholinergic (no slip-ups due to coatings or timing devices), plus Atarax,* one of the best tolerated tranquilizers, to decrease tension without increasing gastric secretion. The result: demonstrated success in 87% of cases.[1]

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Dosage: The usual dosage is one ENARAX 5 or ENARAX 10 tablet twice daily—preferably in the morning and before retiring. Maintenance dose should be adjusted according to therapeutic response. Use with caution in patients with prostatic hypertrophy and only with ophthalmological supervision in glaucoma.

Supplied: ENARAX 5 (oxyphencyclimine HCl 5 mg., Atarax 25 mg.) and ENARAX 10 (oxyphencyclimine HCl 10 mg., Atarax 25 mg.), bottles of 60.

1. Hock, C. W.: Am. J. Gastroenterol. 34:293 (Sept.) 1960.

*brand of hydroxyzine

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In acute and chronic diarrhea the most effective symptomatic solution to the dual problem:

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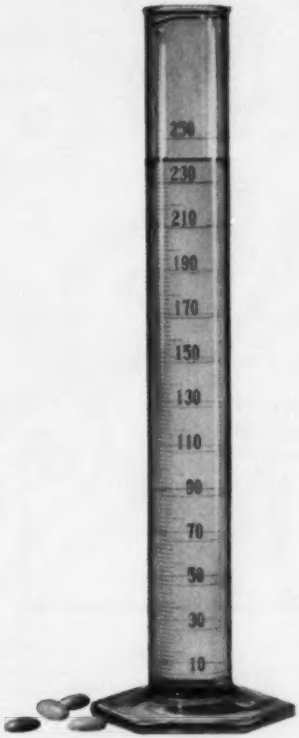
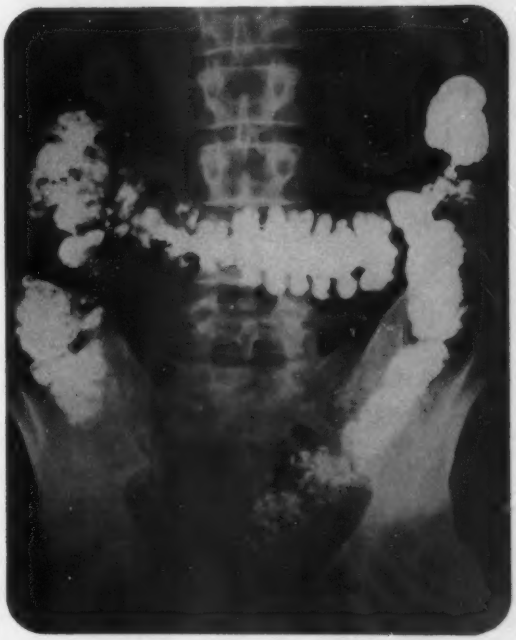
(polycarbophil-thihexinol methylbromide) *tablets*





fast action **1**

for too fluid feces:

Exceptional water-binding capacity of polycarbophil to absorb free fecal water

fast action **2**

for too frequent evacuations:

Superior, yet selective, nonopiate antimotility action of thihexinol methylbromide

(Complete information regarding the use of Sorboquel Tablets is available on request.)

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IN MANY GASTROINTESTINAL DISORDERS,

you may wish to try the simple measures first... dietary control, a good antacid, drastic reduction of smoking and drinking. Some of the less complicated gastrointestinal disorders will respond to this common-sense regimen. On the other hand, in many cases you will decide upon an anticholinergic. And while you're planning the over-all regimen, one conclusion probably becomes inescapable: any lasting improvement depends also on control of the emotional component.

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minimizes gas formation • prevents gas entrapment

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Bevilacqua, R. P.: New York J. Med. 59:4573, 1959.

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Gross, J. M.: J. Internat. Coll. Surgeons 23:34, 1955.

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References: (1) Cohn, E. M.: Am. J. Gastroenterol. *35*:115 (Feb.) 1961. (2) Jones, M. D.; Sakai, H.; and Rogerson, A. G.: J. Pediat. *53*:172 (Aug.) 1958. (3) Machella, T. E.: Gastroenterology *34*:1050 (June) 1958. (4) Orloff, T. L.: Am. J. Roentgenol. *80*:618 (Oct.) 1958. (5) Johnson, C., Jr.; Pearce, C.; and Glenn, F.: Ann. Surg. *152*:91 (July) 1960. (6) McClenahan, J. L.: Pennsylvania M. J. *62*:188 (Feb.) 1959.

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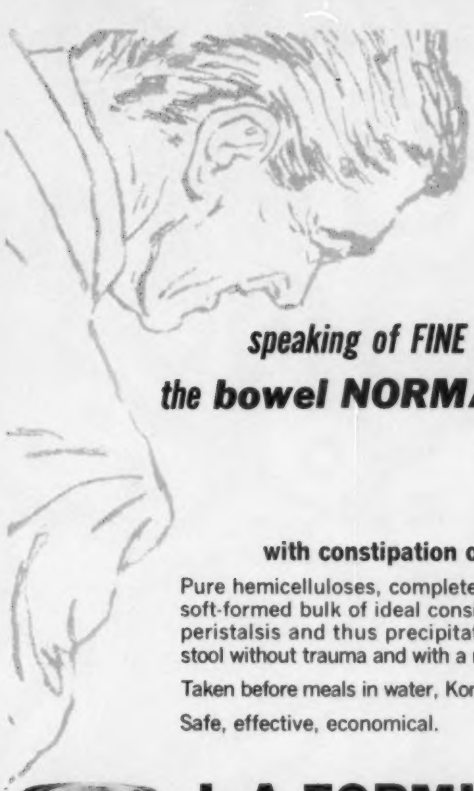

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for the obese patient
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Pure hemicelluloses, completely calorie-free, producing a soft-formed bulk of ideal consistency to stimulate normal peristalsis and thus precipitate easy passage of a bland stool without trauma and with a minimum of peri-anal soiling.

Taken before meals in water, Konsyl helps to depress appetite.

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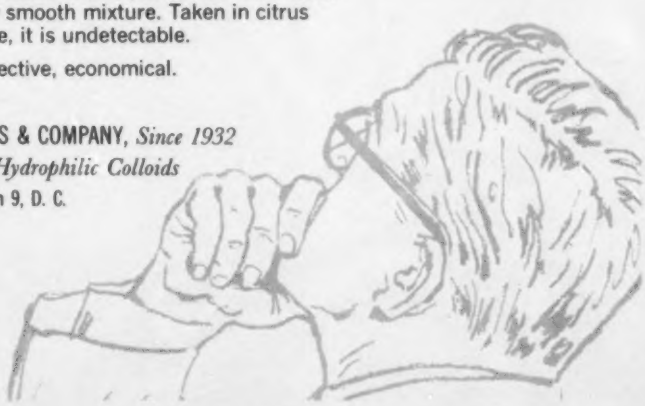

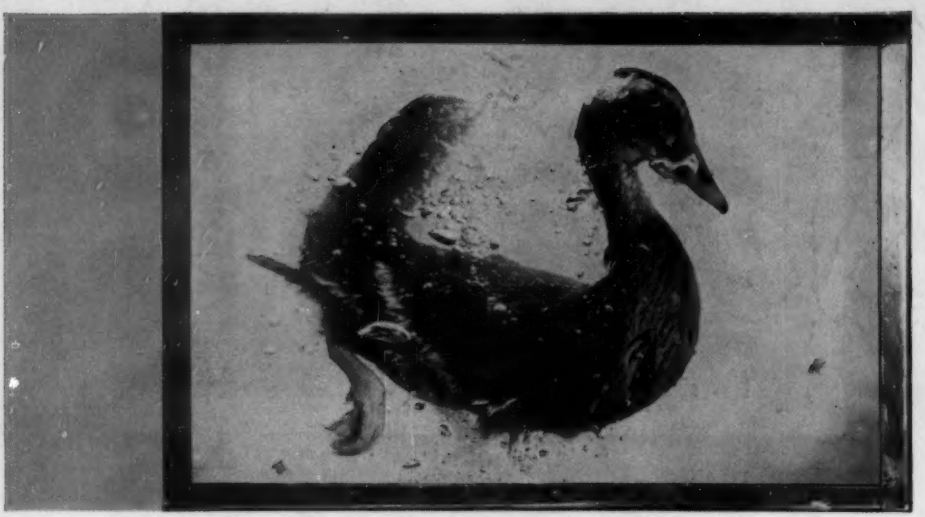

The principle that makes a duck sink... produces soft, normal stools in functional constipation

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Water doesn't roll off this duck's back . . . because the water is Surfak-treated. Surfak decreases interfacial tension between water and oil . . . penetrates the natural oils in the feathers, permits water absorption, adding weight so that the duck sinks.

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